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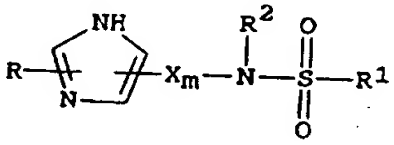
(54) Title: HISTAMINE H_3 RECEPTOR LIGANDS

(57) Abstract

Compounds of formula (I) or (II) wherein R^1 is C_4 to C_{20} hydrocarbyl (in which one or more hydrogen atoms may be replaced by halogen, and up to three carbon atoms may be replaced by oxygen, nitrogen or sulphur atoms, provided that R^1 does not contain an -O-O- group), R^2 is H or C_1 to C_3 alkyl, m is from 1 to 15, n is from 2 to 6, each X group is independently (a), or one X group is $-N(R^4)-$, -O- or -S- and the remaining X groups are independently (a), wherein R^3 is H, C_1 to C_6 alkyl, $-CO_2R^5$, $-CONR^5{}_2$, $-CR^5{}_2OR^6$ or $-OR^5$ (in which R^5 and R^6 are H or C_1 to C_3 alkyl), and R^4 is H or C_1 to C_6 alkyl, each Y group is independently $-C(R^3)R^4-$, or up to two Y groups are $-N(R^4)-$, -O- or -S- and the remaining Y groups are independently $-C(R^3)R^4-$, wherein R^3 is as defined above, one R^4 group in the structure is imidazoyl or imidazoylalkyl and the remaining R^4 groups are H or C_1 to C_6 alkyl, and Z is $> C(R^7)NR^2-$ or > N-, wherein R^7 is any of the groups recited above for R^3, and pharmaceutically acceptable salts thereof are ligands at histamine H_3 receptors.



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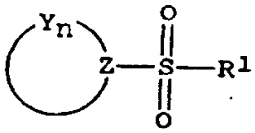

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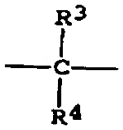

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HISTAMINE H_3 RECEPTOR LIGANDS

This invention relates to compounds which bind to histamine H_3 receptors, and to methods of making such compounds.

Histamine is well known as a mediator in certain hypersensitive reactions of the body, such as allergic rashes, hayfever and asthma. These conditions are now commonly treated with potent antagonists of histamine, so-called "antihistamines".

In the 1940s, it was noted that some physiological effects of histamine, such as increased gastric acid secretion and cardiac stimulation, were not blocked by the anti-histamines which were then available. This led to the proposal that histamine receptors exist in at least two distinct types, referred to as H_1 and H_2 receptors. Subsequently, H_2 antagonists (such as cimetidine, ranitidine and famotidine) were identified, and they have become important in the treatment of gastric ulcers.

In the early 1980s, it was established that histamine also has a role as a neurotransmitter in the central nervous system. Arrang *et al.*, Nature 302, 832 to 837 (1983), proposed the existence of a third histamine receptor subtype (H_3) located presynaptically on histaminergic nerve endings. Arrang *et al.* postulated that the H_3 receptor is involved in inhibiting the synthesis and release of histamine in a negative feedback mechanism. The existence of the H_3 receptor was subsequently confirmed by the development of selective H_3 agonists and antagonists (Arrang *et al.*, Nature 327, 117 to 123 (1987)). The H_3 receptor has subsequently been shown to regulate the release of other neurotransmitters both in the central nervous system and in peripheral organs, in particular in the lungs and GI tract. In addition, H_3 receptors are reported to regulate the release of histamine from mast cells and enterochromaffin-like cells.

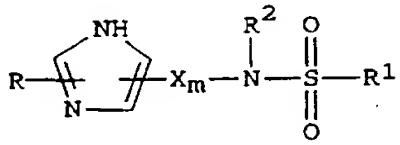
A need exists for potent and selective H_3 ligands (both agonists and antagonists) as tools in the study of the role of histamine as a neurotransmitter, and in its roles as a neuro-, endo- and paracrine hormone. It has also been anticipated that H_3 ligands will

have therapeutic utility for a number of indications including use as sedatives, sleep regulators, anticonvulsants, regulators of hypothalamo-hypophyseal secretion, antidepressants and modulators of cerebral circulation, and in the treatment of asthma and irritable bowel syndrome.

A number of imidazole derivatives have been proposed in the patent literature as H_3 ligands. Representative are the disclosures of EP-A-0197840, EP-A-0214058, EP-A-0458661, EP-A-0494010, EP-A-0531219, WO91/17146, WO92/15567, WO93/01812, WO93/12093, WO93/12107, WO93/12108, WO93/14070, WO93/20061, WO94/17058, WO95/06037, WO95/11894, WO95/14007, US-A-4988689 and US-A-5217986.

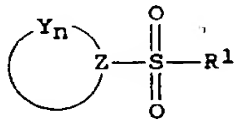
The present invention provides a new class of H_3 receptor ligands, having a sulfonamide or sulfamide group spaced from an imidazole ring.

According to the present invention, there is provided a compound of the formula



I

or



II

wherein R represents from zero to two substituents,

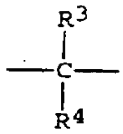
R^1 is C_4 to C_{20} hydrocarbyl (in which one or more hydrogen atoms may be replaced by halogen, and up to four carbon atoms [and especially from 0 to 3 carbon atoms] may be replaced by oxygen, nitrogen or sulphur atoms, provided that R^1 does not contain an -O-O- group),

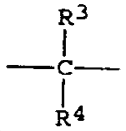
R^2 is H or C_1 to C_{15} hydrocarbyl (in which one or more hydrogen

atoms may be replaced by halogen, and up to three carbon atoms may be replaced by oxygen, nitrogen or sulphur atoms, provided that R^2 does not contain an -O-O- group),

m is from 1 to 15 (preferably 1 to 10, more preferably 3 to 10, eg. 4 to 9)

n is from 2 to 6,

each X group is independently  , or one X group is

$-N(R^4)-$, -O- or -S- (provided that this X group is not adjacent the $-NR^2-$ group) and the remaining X groups are independently  , wherein R^3 is H, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, $-CO_2R^5$, $-CONR^5_2$, $-CR^5_2OR^6$ or $-OR^5$ (in which R^5 and R^6 are H or C_1 to C_3 alkyl), and R^4 is H or C_1 to C_6 alkyl,

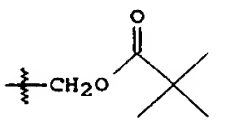
each Y group is independently $-C(R^3)R^4-$, or up to two Y groups are $-N(R^4)-$, -O- or -S- and the remaining Y groups are independently $-C(R^3)R^4-$, wherein R^3 is as defined above, one R^4 group in the structure is imidazoyl, imidazoylalkyl, substituted imidazoyl or substituted imidazoyl, and the remaining R^4 groups are H or C_1 to C_6 alkyl, and

Z is $>C(R^7)NR^2-$ or $>N-$, wherein R^7 is any of the groups recited above for R^3,

and pharmaceutically acceptable salts thereof.

The invention also comprehends derivative compounds ("pro-drugs") which are degraded *in vivo* to yield the species of formula (I) or (II). Pro-drugs are usually (but not always) of lower potency at the target receptor than the species to which they are degraded. Pro-drugs are particularly useful when the desired species has chemical or physical properties which make its administration difficult or inefficient. For example, the desired species may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion of pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", Drug Delivery Systems, pp. 112-176 (1985), and Drugs, 29, pp.455-473 (1985).

Pro-drug forms of the pharmacologically-active compounds of the invention will generally be compounds according to formula (I) or (II) having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the form $-COOR^8$, wherein R^8 is C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl, or one of the following:



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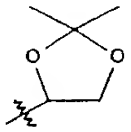


Amidated acid groups include groups of the formula $-CONR^9R^{10}$, wherein R^9 is H, C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, or substituted benzyl, and R^{10} is -OH or one of the groups just recited for R^9.

Compounds of formula (I) or (II) having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This will hydrolyse with first order kinetics in aqueous solution.

Pharmaceutically acceptable salts of the acidic compounds of the invention include salts with alkali metals and alkaline earth metals, such as sodium, potassium, calcium and magnesium, and salts with organic bases. Suitable organic bases include amines such as N-methyl-D-glucamine.

Pharmaceutically acceptable salts of the basic compounds of the invention include salts

derived from organic or inorganic acids. Suitable acids include hydrochloric acid, hydrobromic acid, trifluoracetic acid, phosphoric acid, oxalic acid, maleic acid, succinic acid and citric acid.

The compounds of the invention may exist in various enantiomeric, diastereomeric and tautomeric forms. It will be understood that the invention comprehends the different enantiomers, diastereomers and tautomers in isolation from each other, as well as mixtures of enantiomers, diastereomers and tautomers.

The term "hydrocarbyl", as used herein, refers to monovalent groups consisting of carbon and hydrogen. Hydrocarbyl groups thus include alkyl, alkenyl, and alkynyl groups (in both straight and branched chain forms), cycloalkyl (including polycycloalkyl), cycloalkenyl, and aryl groups, and combinations of the foregoing, such as alkylaryl, alkenylaryl, alkynylaryl, cycloalkylaryl, and cycloalkenylaryl groups,

A "carbocyclic" group, as the term is used herein, comprises one or more closed chains or rings, which consist entirely of carbon atoms. Included in such groups are alicyclic groups (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and adamantyl), groups containing both alkyl and cycloalkyl moieties (such as adamantanemethyl), and aromatic groups (such as phenyl, naphthyl, indanyl, fluorenyl, (1,2,3,4)-tetrahydronaphthyl, indenyl and isoindenyl).

The term "aryl" is used herein to refer to aromatic carbocyclic groups, including those mentioned above.

A "heterocyclic" group comprises one or more closed chains or rings which have at least one atom other than carbon in the closed chain or ring. Examples include benzimidazolyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl,

indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl.

When reference is made herein to a substituted carbocyclic group (such as substituted phenyl) or a substituted heterocyclic group, the substituents are preferably from 1 to 3 in number and selected from C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 alkylthio, carboxy, C_1 to C_6 carboalkoxy, nitro, trihalomethyl, hydroxy, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, aryl, C_1 to C_6 alkylaryl, halo, sulphamoyl and cyano. The moiety R, when present, may represent one or two of the foregoing groups, and preferably C_1 to C_3 alkyl or halo.

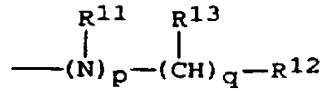
The term "halogen", as used herein, refers to any of fluorine, chlorine, bromine and iodine.

Preferably, R^2 is selected from H, C_1 to C_6 alkyl, C_1 to C_6 cycloalkyl, C_1 to C_6 hydroxyalkyl, C_1 to C_6 alkylhydroxyalkyl, aryl C_1 to C_6 alkyl and substituted aryl C_1 to C_6 alkyl. For example, R^2 may be H or C_1 to C_3 alkyl.

In certain embodiments, $-X_m-$ is a C_1 to C_8 alkylene group, eg a butylene group.

Included in the definition of R^1 are aryl-containing groups (such as phenyl, substituted phenyl, naphthyl and substituted naphthyl), and (cycloalkyl)alkyl groups (such as cyclohexylpropyl and adamantylpropyl).

Preferably, R^1 is a group of the formula



III

wherein

p is 0 or 1,

R^{11} is H or C_1 to C_3 alkyl,

q is from 0 to 4,

R^{12} is a carbocyclic, substituted carbocyclic, heterocyclic or substituted heterocyclic group, and

R^{13} is independently selected from H, C_1 to C_6 alkyl, C_1 to C_6 cycloalkyl, C_1 to C_6 hydroxyalkyl, C_1 to C_6 alkylhydroxyalkyl, aryl C_1 to C_6 alkyl and substituted aryl C_1 to C_6 alkyl.

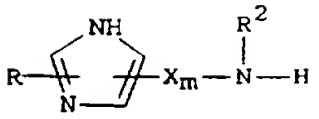
Preferably, R^{13} is hydrogen.

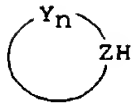
Imidazoylalkyl groups in the compounds of the invention usually have from 1 to 8 carbon atoms in the alkyl chain.

We have found that a number of compounds in the prior art have shown a significant discrepancy in their activity as measured by two ileum based assays which are described below. Analysis of data obtained in these particular functional and radioligand binding assays and also in other related bioassays suggests that the discrepancy may be connected, at least in part, with residual efficacy inherent in these structures. In practice, this means that these particular compounds may act as agonists, at least in some tissues.

Surprisingly, we have found that when m is 3 or more, preferably from 3 to 9, and especially from 4 to 8, the compounds disclosed herein do not show a significant discrepancy in the two assays. Thus, these compounds may be considered to be true antagonists with respect to the action of the native hormone, rather than having the potential to act as partial or full agonists. In one aspect, therefore, the present invention provides the use of these compounds as histamine antagonists, and in the manufacture of medicaments for this purpose.

The compounds of the invention which are sulfonamides may be prepared by reacting a suitably protected derivative of a compound of the formula



or 

IV

with a sulfonyl chloride of the formula R^1SO_2Cl. Suitable protecting groups for the imidazole moiety include trityl and *N,N*-dimethylsulfamoyl groups. Any other functional groups in the reactants may be protected by reagents well known to those in the art.

The reaction with the sulfonyl chloride is carried out in a suitable non-aqueous solvent such as dried *N,N*-dimethylformamide or dried dichloromethane, in the presence of a base such as triethylamine. Typically, the reaction is carried out at room temperature for a period of several hours.

Compounds of the invention which are sulfamides may conveniently be prepared by

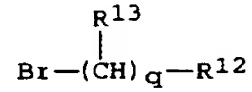
a) reacting chlorosulfonyl isocyanate with an appropriate alcohol of the formula $R^{14}OH$,

b) reacting the product of step a) with a suitably protected derivative of a compound of formula IV above,

c) reacting the product of step b) with a base such as sodium hydride and then a compound of formula R^1-Br, wherein the bromine atom is attached to a carbon atom of R^1, and

d) treating the product of step c) with acid to remove the $R^{14}OCO$- group, and other protecting groups.

In preferred embodiments, the reagent in step c) is of the formula



wherein q, R^{12} and R^{13} are as defined above.

Particularly preferred alcohols for use in step a) are *t*-butanol and benzyl alcohol.

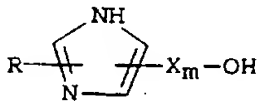
Figure 1 illustrates the synthesis of N-[5-(4(5)-imidazoyl)pentyl]-N'-(4-chlorophenyl)-methyl-sulfamide by this method.

In an alternative process, sulfamides according to invention may be prepared by

a) reacting chlorosulfonyl isocyanate with an appropriate alcohol of the formula $R^{14}OH$,

b) reacting the product of step a) with a suitably protected derivative of a compound of the formula R^1-H, wherein the hydrogen atom is attached to a nitrogen atom of R^1,

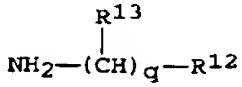
c) reacting the product of step b) with a suitably protected derivative of a compound of formula



and

d) treating the product of step c) with acid to remove the $R^{14}OCO$- group, and other protecting groups.

In preferred embodiments, the reagent used in step b) is of the formula



wherein q, R^{12} and R^{13} are as defined above. Figure 2 illustrates the synthesis of N-[4-(4(5)-imidazoyl)butyl]-N'-cyclohexylmethylsulfamide by this method.

Pharmaceutically acceptable salts of the acidic or basic compounds of the invention can of course be made by conventional procedures, such as by reacting the free base or acid with at least a stoichiometric amount of the desired salt-forming acid or base.

It is anticipated that the compounds of the invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical administration.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

Effective doses of the compounds of the present invention may be ascertained by conventional methods. The specific dosage level required for any particular patient will depend on a number of factors, including the severity of the condition being treated, the route of administration and the weight of the patient. In general, however, it is anticipated that the daily dose (whether administered as a single dose or as divided doses) will be in the range 0.001 to 5000 mg per day, more usually

from 1 to 1000 mg per day, and most usually from 10 to 200 mg per day. Expressed as dosage per unit body weight, a typical dose will be expected to be between 0.01 μg/kg and 50 mg/kg, especially between 10 μg/kg and 10 mg/kg, eg. between 100 μg/kg and 2 mg/kg.

The invention is now further illustrated by means of the following examples.

EXAMPLE 1

N-[2-(4(5)-Imidazoyl)ethyl]-2-naphthalenesulfonamide

To a suspension of histamine (824mg, 7.41mmol) in dried *N,N*-dimethylformamide (10ml) was added triethylamine (2.07ml, 14.8mmol) and 2-naphthalenesulfonyl chloride (1.68g, 7.41mmol). The mixture was stirred at room temperature for 48h, poured into water (50ml) and extracted with ethyl acetate (3x20ml). The combined organic extracts were washed with brine (3x20ml), the solvent evaporated under reduced pressure and the residue purified by flash column chromatography (silica, 1% NH_3 aq (880)/10%MeOH/CH_2Cl_2). The resultant oil (R_f 0.17) was crystallized from tetrahydrofuran to afford the title compound as a white solid, (440mg, 20%): ^1H NMR (300Hz, d_6-DMSO) 11.73(1H, s), 8.41 (1H, s), 8.13(2H, m), 8.02(1H, d), 7.80(1H, dd), 7.67(2H, m), 7.44(1H, d), 6.74(1H, s), 2.99(2H, t), 2.58(2H, t). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 54.67, H 4.69, N 10.07%; $C_{19}H_{19}N_3O_6S$ requires: C 54.67, H 4.59, N 10.07%.

EXAMPLE 2

N-[2-(4(5)-Imidazoyl)ethyl]-benzenesulfonamide

Step a. *N-[2-(1-benzenesulfonyl-imidazol-4-yl)ethyl]-benzenesulfonamide.* To a suspension of histamine (337mg, 3.04mmol) in dried dichloromethane (60ml) was added triethylamine (1.27ml, 9.10mmol) and benzenesulfonyl chloride (775μl, 6.08mmol). The mixture was stirred at room temperature for 6h, the solvent

evaporated under reduced pressure and the residue taken up in ethyl acetate (50ml). The triethylamine hydrochloride was filtered off and the filtrate evaporated under reduced pressure. The residue was crystallised from ethyl acetate/hexane to afford the product as a white solid (1.04g, 93%).

Step b. To a suspension of the product of step a (1.04g, 2.82mmol) in ethanol (115ml) was added a solution of sodium carbonate (1.20g, 11.3mmol) in water (85ml). The mixture was stirred for 24h and the ethanol removed under reduced pressure at ambient temperature. The aqueous mixture was extracted with chloroform (6x50ml), and the combined extracts were washed with brine and dried over anhydrous sodium sulfate. Filtration and evaporation under reduced pressure afforded the title compound as a white solid (567mg, 80%): ^{1}H NMR (300Hz, d_6-DMSO) 7.77(2H, m), 7.60(3H, m), 7.46(1H, s), 6.74(1H, s), 2.94(2H, t), 2.57(2H, t). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 46.65, H 4.74, N 10.95%; $C_{15}H_{17}N_3O_6S$ .1.0H_2O requires: C 46.77, H 4.97, N 10.91%.

EXAMPLE 3

N-[2-(4(5)-Imidazoyl)ethyl]-1-naphthalenesulfonamide

Step a. *N-[2-(1-(1-naphthalenesulfonyl)-4-imidazoyl)ethyl]-1-naphthalenesulfonamide.* To a suspension of histamine (393mg, 3.54mmol) in dried dichloromethane (60ml) was added triethylamine (1.48ml, 10.6mmol) and 1-naphthalenesulfonyl chloride (2.01g, 8.85mmol). The mixture was stirred at room temperature for 18h, the solvent evaporated under reduced pressure and the residue taken up in ethyl acetate (100ml). The triethylamine hydrochloride was removed by filtration and the filtrate evaporated under reduced pressure. Flash column chromatography (silica, 70% ethyl acetate/hexane) gave the product (R_f 0.35) as a colourless foam (1.32g, 76%).

Step b. To a solution of the product of step a (1.18g, 2.41mmol) in ethanol (100ml) was added a solution of sodium carbonate (1.02g, 9.64mmol) in water (35ml). The

mixture was stirred for 18h and the insoluble material removed by filtration. The ethanol was evaporated under reduced pressure at ambient temperature. The precipitate thus formed was collected by filtration and dried in vacuo at 50°C. Flash column chromatography (silica, 1% NH_3 aq (880)/10%MeOH/CH_2Cl_2) afforded the title compound (R_f 0.29) as a white solid (366mg, 50%): ^{1}H NMR (300Hz, d_6-DMSO) 11.70(1H, br s), 8.64(1H, dd), 8.21(1H, d), 8.09(2H, m), 8.03(1H, t), 7.68(3H, m), 7.42(1H, d), 6.66(1H, s), 2.97(2H, m), 2.55(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 53.42, H 4.73, N 9.69%; $C_{19}H_{19}N_3O_6S.0.6H_2O$ requires: C 53.31, H 4.75, N 9.82%.

EXAMPLE 4

N-[2-(4(5)-Imidazoyl)ethyl]-3-cyclohexylpropanesulfonamide

Step a. *3-Cyclohexylpropanesulfonyl chloride.* A mixture of 1-chloro-3-cyclohexylpropane (8.00g, 50mmol), thiourea (3.80g, 50mmol) and sodium iodide (100mg) in ethanol (40ml) was heated at reflux for 3h. The solvent was evaporated under reduced pressure and the residue triturated with diethyl ether. The product was collected by filtration, washed with diethyl ether and air dried to afford a white solid (6.64g), which was suspended in water (50ml)/dichloromethane (50ml). With vigorous stirring chlorine gas was bubbled through the mixture for 30min, maintaining the temperature below 20°C. The organic layer was separated, washed with ice-cold 10% sodium bisulfite aq. (2 x 50ml), saturated sodium hydrogencarbonate aq. (2 x 50ml) and water (50ml), and dried over magnesium sulfate. Filtration and evaporation afforded the product as a colourless oil (3.60g, 34%).

Step b. To a suspension of histamine (222mg, 2.00mmol) in dichloromethane (10ml) was added triethylamine (278μl, 2.00mmol) and a solution of the product of step a (224mg, 1.00mmol) in dichloromethane (2ml) dropwise over 5min. The mixture was stirred for 18h and the solvent evaporated under reduced pressure to give a white solid. Flash column chromatography (silica, 1% NH_3 aq (880)/10%MeOH/CH_2Cl_2)

afforded the title compound (R_f 0.25) as a colourless oil (100mg, 33%): ^{1}H NMR (300Hz, $CDCl_3$) 8.80(1H, br s), 7.52(1H, dd), 6.83(1H, s), 5.80(1H, br s), 3.38(2H, t), 2.93(2H, t), 2.84(2H, t), 1.78(2H, m), 1.65(5H, m), 1.25(6H, m), 0.88(2H, m).

EXAMPLE 5

N-[2-(4(5)-Imidazoyl)ethyl]-(3-(1-adamantyl)propane)sulfonamide

3-(1-Adamantyl)propanesulfonyl chloride (700mg, 2.50mmol), prepared by the procedure Example 4 step a, was reacted with histamine (555mg, 5.00mmol) according to the method for Example 4 step b. Thus, the title compound was obtained as a colourless foam (340mg, 39%): ^{1}H NMR (300Hz, $CDCl_3$) 7.55(1H, s), 6.86(1H, s), 5.50(1H, br s), 3.41(2H, t), 2.93(2H, t), 2.86(2H, t), 1.94(3H, s), 1.80-1.59(8H, m), 1.46(6H, s), 1.12(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 55.55, H 7.20, N 8.83%; $C_{22}H_{33}N_3O_6S.0.5H_2O$ requires: C 55.44, H 7.19, N 8.82%.

EXAMPLE 6

N-[5-(4(5)-Imidazoyl)pentyl]-2-naphthalenesulfonamide

Step a. *N-[5-(1-(N',N'-Dimethylsulfamoyl)-imidazol-4-yl)pentyl]-2-naphthalenesulfonamide.* To a solution of 5-(5-aminopentyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] (166mg, 0.64mmol) and triethylamine (107μl, 0.77mmol) in dry dichloromethane (2ml), cooled in ice under an atmosphere of argon, was added 2-naphthalenesulfonyl chloride (175mg, 0.77mmol). The solution was stirred for 45min at 0°C and the solvent evaporated. Flash column chromatography (silica; 0.5:5:95 ammonia(880)/methanol/dichloromethane) of the residue afforded the product (R_f 0.76) as a colourless foam (224mg, 79%).

Step b. A solution of the product from step a (224mg, 0.50mmol) in a mixture of ethanol (4ml) and 1M hydrochloric acid (4ml) was heated at reflux for 6h and the

solvent removed *in vacuo*. Flash column chromatography (silica; 0.5:5:95-1:10:90 ammonia(880)/ methanol/dichloromethane) of the residue afforded the title compound (R_f 0.26; 1:10:90 ammonia(880)/methanol/dichloromethane) as a colourless foam (138mg, 81%): ^{1}H NMR (300Hz, d_6-DMSO) 11.74(1H, br s), 8.41 (1H, d), 8.13(2H, t), 8.02(1H, d), 7.80(1H, dd), 7.67(3H, m), 7.44(1H, s), 6.61(1H, s), 2.79(2H, dd), 2.37(2H, t), 1.40(4H, m), 1.22(2H, dd). Found: C 63.04, H 6.22, N 12.19%; $C_{18}H_{21}N_3O_2S$ requires: C 62.95, H 6.16, N 12.23%.

EXAMPLE 7

N-*[4-(4(5)-Imidazoyl)butyl]-2-naphthalenesulfonamide*

Step a. *4-(4-Chlorobutyl)-1-(triphenylmethyl)-imidazole.* A solution of 5-(4-chlorobutyl)-2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] (8.80g, 23.2mmol) in a mixture of ethanol (100ml) and 2M hydrochloric acid (100ml) was heated at reflux for 2h. The ethanol was evaporated and the aqueous solution extracted with diethyl ether (2x50ml). The aqueous layer was evaporated and the residue dissolved in dry dichloromethane (100ml). Triethylamine (6.50ml, 46.6mmol) and triphenylmethyl chloride (7.10g, 25.5mmol) were added, the solution stirred for 18h, washed with water and dried over magnesium sulfate. Filtration and evaporation gave a brown oil. Flash column chromatography (silica; 5% methanol/dichloromethane) of the residue afforded the product as a yellow oil (7.20g, 77%).

Step b. *4-(4-Phthalimidobutyl)-1-(triphenylmethyl)-imidazole.* Potassium phthalimide (1.67g, 9.00mmol) was added to a solution of the product from step b (7.20g, 18.0mmol) in dry *N,N*-dimethylformamide (50ml), under an atmosphere of argon. The mixture was stirred and heated at 100°C for 5h, allowed to cool to room temperature and poured onto ice/water (150ml). The resultant white precipitate was collected by filtration. The residue was dissolved in dichloromethane (100ml), washed brine and dried over magnesium sulfate. The solvent was evaporated and the residue purified by flash column chromatography (silica; 5% methanol/dichloromethane), from which the product was isolated as a yellow oil (4.50g, 98%).

Step c. *4-(4-Aminobutyl)-1-(triphenylmethyl)-imidazole.* To a suspension of the product from step 8 (3.00g, 5.86mmol) in ethanol (30ml) was added hydrazine hydrate (1.5ml, 25.8mmol). The mixture was heated at reflux for 2h and allowed to cool to room temperature. The preciptate was removed by filtration. The filtrate was evaporated and the residue triturated with chloroform. The solid material was again removed by filtration. The filtrate was evaporated and the trituration process repeated to give the product as a yellow oil (2.05g, 92%).

Step d. N-*[4-(1-(Triphenylmethyl)-imidazol-4-yl)butyl]-2-naphthalenesulfonamide.* To a solution of the product from step c (465mg, 1.22mmol) and triethylamine (185μl, 1.33mmol) in dry dichloromethane (15ml) was added 2-naphthalenesulfonyl chloride (227mg, 1.22mmol). The solution was stirred for 2h and the solvent evaporated. Flash column chromatography (silica; 5% methanol/dichloromethane) of the residue afforded the product as a colourless foam (588mg, 84%).

Step e. A solution of the product from step d (588mg, 1.02mmol) in trifluoroacetic acid (5ml) was stirred for 18h and the solvent evaporated. Flash column chromatography (silica; 1:10:90 ammonia(880)/methanol/dichloromethane) of the residue afforded the title compound (R_f 0.24) as a white solid (96mg, 63%): ^{1}H NMR (300Hz, d_6-DMSO) 11.70(1H, br s), 8.41 (1H, s), 8.13(2H, t), 8.03(1H, d), 7.80(1H, dd), 7.67(3H, m), 7.45(1H, s), 6.62(1H, s), 2.76(2H, dd), 2.38(2H, t), 1.48(2H, m), 1.41(2H, dd). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 56.55, H 5.31, N 9.31%; $C_{21}H_{23}N_3O_6S.0.5H_2O$ requires: C 56.62, H 5.20, N 9.43%.

EXAMPLE 8

N-*[6-(4(5)-Imidazoyl)hexyl]-2-naphthalenesulfonamide*

The title compound was prepared according to the procedure for Example 6, using 5-(6-aminohexyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a. The product of the two steps was obtained as white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.72(1H, br s), 8.41 (1H, d), 8.13(2H, dd), 8.03(1H, d), 7.80(1H, dd), 7.67(3H,

m), 7.44(1H, s), 6.62(1H, s), 2.74(2H, dd), 2.37(2H, t), 1.42(2H, m), 1.33(2H, m), 1.17(4H, m). Found: C 60.99, H 6.59, N 11.17%; $C_{19}H_{23}N_3O_2S.0.9H_2O$ requires: C 61.07, H 6.69, N 11.24%.

EXAMPLE 9

N-[5-(4(5)-Imidazoyl)pentyl]-(4-chlorophenyl)methanesulfonamide

Step a. *N-[5-(1-(N',N'-Dimethylsulfamoyl)-imidazol-4-yl)pentyl]-(4-chlorophenyl) methanesulfonamide.* To a solution of 5-(5-aminopentyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] (412mg, 1.58mmol) and triethylamine (264μl, 1.90mmol) in dry dichloromethane (5ml), cooled under an atmosphere of argon to -78°C, was added dropwise a solution of (4-chlorophenyl)methanesulfonyl chloride (533mg, 2.37mmol) in dry dichloromethane (5ml). The resultant solution was stirred for 18h, allowing to warm to room temperature, and the solvent evaporated. Flash column chromatography (silica; 0.5:5:95 ammonia(880)/methanol/dichloromethane) of the residue afforded the product (R_f 0.66; 1:10:90 ammonia(880)/methanol/ dichloromethane) as a colourless oil (307mg, 43%).

Step b. A solution of the product from step a (275mg, 0.61mmol) in a mixture of ethanol (4ml) and 1M hydrochloric acid (4ml) was heated at reflux for 18h and the solvent removed *in vacuo*. Flash column chromatography (silica; 1:10:90 ammonia(880)/ methanol/dichloromethane) of the residue afforded the product (R_f 0.34; 1:10:90 ammonia(880)/ methanol/dichloromethane) as a white crystalline solid (181mg, 87%): ^{1}H NMR (300Hz, d_6-DMSO) 11.75(1H, br s), 7.46(1H, s), 7.43(2H, dd), 7.37(2H, d), 7.04(1H, t), 6.68(1H, s), 4.31(2H, s), 2.87(2H, dd), 2.45(2H, t), 1.50(2H, m), 1.40(2H, m), 1.27(2H, m). Found: C 52.88, H 6.13, N 12.28%; $C_{15}H_{20}ClN_3O_2S$ requires: C 52.70, H 5.90, N 12.29%.

EXAMPLE 10

N-[4-(4(5)-Imidazoyl)butyl]-(4-chlorophenyl)methanesulfonamide

The title compound was prepared according to the procedure for Example 9, using 4-

(4-aminobutyl)-1-(triphenylmethyl)-imidazole (Example 7 step c) as the substrate in step a. The product of the two steps was obtained as white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.47(1H, s), 7.43(2H, dd), 7.37(2H, d), 7.05(1H, t), 6.69(1H, s), 4.31(2H, s), 2.89(2H, dd), 2.46(2H, t), 1.55(2H, m), 1.45(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 48.68, H 5.14, N 9.32%; $C_{18}H_{22}ClN_3O_6S$ requires: C 48.70, H 5.00, N 9.47%.

EXAMPLE 11

N-[6-(4(5)-Imidazoyl)hexyl]-(4-chlorophenyl)methanesulfonamide

The title compound was prepared according to the procedure for Example 9, using 5-(6-aminohexyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a. The product of the two steps was obtained as a white crystalline solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.71(1H, br s), 7.46(1H, s), 7.43(2H, ddd), 7.37(2H, ddd), 7.05(1H, t), 6.68(1H, s), 4.31(2H, s), 2.86(2H, dd), 2.46(2H, t), 1.52(2H, m), 1.37(2H, m), 1.27(4H, m). Found: C 51.51, H 6.28, N 15.05%; $C_{16}H_{22}ClN_3O_2S$ requires: C 51.81, H 6.25, N 15.11%.

EXAMPLE 12

N-[5-(4(5)-Imidazoyl)pentyl]-N'-(4-chlorophenyl)methyl-sulfamide

Step a. *N-[5-(1-(N'',N''-Dimethylsulfamoyl)-imidazol-4-yl)pentyl]-N'-tert-butoxycarbonyl-sulfamide.* To a solution of chlorosulfonyl isocyanate (211μl, 2.42mmol) in dry dichloromethane (3ml), cooled in ice under an atmosphere of argon, was added dropwise a solution of dry *t*-butanol (346μl, 3.63mmol) in dry dichloromethane (3ml). The solution was allowed to warm to room temperature, stirred for 10min and added dropwise, under argon, to an ice-cooled solution of 5-(5-aminopentyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] (484mg, 1.86mmol) and triethylamine (388μl, 2.79mmol) in dry dichloromethane (6ml). The mixture was stirred for 18h, allowing to warm to room temperature, and the solvent evaporated. Flash column chromatography (silica; 0.5:5:95

ammonia(880)/methanol/dichloromethane) of the residue afforded the product (R_f 0.29; 1:10:90 ammonia(880)/methanol/dichloromethane) as a colourless oil (400mg, 49%).

Step b. N'-*(4-Chlorophenyl)methyl*-N-*[5-(1-(*N'',N''*-dimethylsulfamoyl)-imidazol-4-yl)pentyl]*-N'-tert-*butoxycarbonyl-sulfamide*. To a solution of the product from step a (390mg, 0.89mmol) and 4-chlorobenzyl bromide (183mg, 0.89mmol) in dry *N,N*-dimethylformamide (3ml), cooled under an atmosphere of argon to -15°C, was added sodium hydride (36mg, 0.89mmol, 60% dispersion in oil). The mixture was stirred for 18h, allowing to warm slowly to ambient temperature. Water (15ml) was added and the mixture was extracted with ethyl acetate (4x10ml). The combined organics were washed four times with water, dried over sodium sulfate and evaporated. Flash column chromatography (silica; 0.2:2:98 ammonia(880)/methanol/dichloromethane) of the residue afforded the product (R_f 0.29; 1:10:90 ammonia(880)/methanol/dichloromethane) as a colourless oil (378mg, 75%).

Step c. A suspension of the product from step b (374mg, 0.66mmol) in a mixture of ethanol (5ml) and 1M hydrochloric acid (5ml) was heated at reflux for 18h and the solvent removed *in vacuo*. Flash column chromatography (silica; 1:10:90 ammonia(880)/methanol/dichloromethane) of the residue afforded the product (R_f 0.24) as a white solid (132mg, 56%): ^{1}H NMR (300Hz, d_6-DMSO) 7.46(1H, s), 7.43(5H, m), 6.87(1H, t), 6.68(1H, s), 4.03(2H, d), 2.78(2H, dd), 2.45(2H, t), 1.58(2H, m), 1.47(2H, m), 1.27(2H, m). Found: C 50.33 H 5.88, N 15.55%; $C_{15}H_{21}ClN_4O_2S$ requires: C 50.48, H 5.93, N 15.70%.

EXAMPLE 13

N-*[4-(4(5)-Imidazoyl)butyl]*-N'-*(4-chlorophenyl)methyl-sulfamide*

The title compound was prepared according to the procedure for Example 12, using 4-(4-aminobutyl)-1-(triphenylmethyl)-imidazole (Example 7 step c) as the substrate in step a. The product of the three steps was obtained as white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.68(1H, br s), 7.47(1H, d), 7.36(4H, m), 6.86(1H, t), 6.68(1H, s),

3.98(2H, d), 2.79(2H, dd), 2.45(2H, t), 1.53(2H, m), 1.43(2H, m). Found: C 49.08 H 5.61, N 16.23%; $C_{14}H_{19}ClN_4O_2S$ requires: C 49.05, H 5.59, N 16.34%.

EXAMPLE 14

N-*[3-(4(5)-Imidazoyl)propyl]*-N'-*(4-chlorophenyl)methyl-sulfamide*

Step a. *4-(3-Phthalimidopropyl)-1-(triphenylmethyl)-imidazole.* To a solution of 3-[1-(triphenylmethyl)imidazol-4-yl]propan-1-ol[3] (2.24g, 6.07mmol) in dry tetrahydrofuran (10ml), under an argon atmosphere, was added phthalimide (1.16g, 7.89mmol) and triphenylphosphine (2.07g, 7.89mmol). The suspension was cooled in ice and a solution of diethylazodicarboxylate (1.24ml, 7.89mmol) in dry tetrahydrofuran (10ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 2h. Diethyl ether (20 ml) was added. The precipitate was collected by filtration and dried *in vacuo* to afford a white solid (2.08g, 68%).

Step b. *4-(3-Aminopropyl)-1-(triphenylmethyl)-imidazole.* To a suspension of the product from step a (4.09g, 8.22mmol) in ethanol (82ml) was added hydrazine hydrate (2.32ml, 41.1mmol). The mixture was heated at reflux for 3h and allowed to cool to room temperature. The preciptate was removed by filtration. The filtrate was evaporated and the residue triturated with chloroform. The solid material was again removed by filtration. The filtrate was evaporated and the trituration process repeated to give the product as a yellow oil in quantitative yield.

Step c. N-*[3-(1-(triphenylmethyl)-imidazol-4-yl)propyl]*-N'-tert-*butoxycarbonyl*-N'-*(4-chlorophenyl)methyl-sulfamide* . The product from step b was converted to the product according to the procedure of Example 12 steps a and b.

Step d. A solution of the product from step c (308mg, 0.46mmol) in trifluoroacetic acid (3ml) was stirred for 18h and the solvent evaporated. Flash column chromatography (silica; 1:10:90 ammonia(880)/methanol/dichloromethane) of the residue afforded the title compound (R_f 0.18) as a white solid (96mg, 63%): ^1H NMR (300Hz, d_6-DMSO) 11.77(1H, br s), 7.37(4H, m), 6.99(1H, t), 6.72(1H, s),

3.98(2H, d), 2.81(2H, dd), 2.48(2H, m), 1.72(2H, m). Found: C 47.30, H 5.26, N 16.95%; $C_{13}H_{17}ClN_4O_2S$ requires: C 47.49, H 5.21, N 17.04%.

EXAMPLE 15

N-[6-(4(5)-Imidazoyl)hexyl]-N'-(4-chlorophenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(6-aminohexyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a. The product of the three steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.46(1H, d), 7.35(5H, m), 6.86(1H, t), 6.67(1H, s), 3.98(2H, d), 2.75(2H, dd), 2.45(2H, t), 1.52(2H, m), 1.38(2H, m), 1.25(4H, m). Found: C 51.51, H6.28, N 15.05%; $C_{16}H_{23}ClN_4O_2S$ requires: C 51.81, H 6.25, N 15.11%.

EXAMPLE 16

N-[2-(4(5)-Imidazoyl)ethyl]-3,4-dichlorobenzenesulfonamide

The title compound was prepared according to the procedure for Example 2, using histamine and 3,4-dichlorobenzenesulfonyl chloride (prepared essentially as Example 4 step a) as the substrates in step a. The product of the two steps was obtained as a white crystalline solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.80(1H, br s), 7.94(1H, d), 7.90(1H, m), 7.87(1H, m), 7.72(1H, dd), 7.47(1H, s), 6.76(1H, s), 3.00(2H, t), 2.59(2H, t).

EXAMPLE 17

N-[2-(4(5)-Imidazoyl)ethyl]-2-phenylethanesulfonamide

Step a. *4-(2-Phthalimidoethyl)-1-(triphenylmethyl)-imidazole.* To a suspension of 4(5)-(2-phthalimidoethyl)-imidazole[2] (838mg, 3.48mmol) in dry dichloromethane (10ml), under an argon atmosphere, was added triethylamine (728μl, 5.22mmol) and triphenylmethyl chloride (1.16g, 4.18mmol). Flash column chromatography (silica; 0.2:2:98 to 1:10:90 ammonia(880)/methanol/dichloromethane) of the residue afforded the product as a foam (1.20g, 71%).

Step b. *4-(2-Aminoethyl)-1-(triphenylmethyl)-imidazole.* To a suspension of the product from step a (1.20g, 2.48mmol) in ethanol (25ml) was added hydrazine hydrate (702 ml, 12.4mmol). The mixture was heated at reflux for 90min and allowed to cool to room temperature. The preciptate was removed by filtration. The filtrate was evaporated and the residue triturated with chloroform. The solid material was again removed by filtration. The filtrate was evaporated and the trituration process repeated to give the product as a yellow oil (818mg, 93%).

Step c. N-*[2-(1-(Triphenylmethyl)imidazoyl-4-yl))ethyl]-2-phenylethanesulfonamide.* To a solution of the product from step b (353mg, 1.00mmol) and triethylamine (154μl, 1.10mmol) in dry dichloromethane (5ml) was added a solution of 2-phenylethanesulfonyl chloride (prepared essentially as Example 4 step a) (205mg, 1.00mmol) in dry dichloromethane (2ml). The solution was stirred for 30min, washed with water and dried over magnesium sulfate. Filtration and evaporation afforded the product (R_f 0.68; 1:10:90 ammonia(880)/methanol/dichloromethane) as a white solid (450mg, 86%).

Step d. A solution of the product from step c (440mg, 0.84mmol) in trifluoroacetic acid (4ml) was stirred for 18h and the solvent evaporated. Flash column chromatography (silica; 1:10:90 ammonia(880)/methanol/dichloromethane) of the residue afforded the title compound (R_f 0.25) as an oil (61mg, 26%): ^{1}H NMR (300Hz, $CDCl_3$) 7.83(1H, s), 7.20(5H, m), 6.93(1H, s), 3.39(2H, m), 3.27(2H, m), 3.08(2H, m), 2.88(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 51.35, H 5.41, N 10.62%; $C_{17}H_{21}N_3O_6S$ requires: C 51.64, H 5.35, N 10.63%.

EXAMPLE 18

N-[2-(4(5)-Imidazoyl)ethyl]-3-phenylpropanesulfonamide

The title compound was prepared according to the procedure for Example 17, using 3-phenylpropanesulfonyl chloride (prepared essentially as Example 4 step a) as the substrate in step c. The product (R_f 0.26; 1:10:90

ammonia(880)/methanol/dichloromethane) of the four steps was obtained as a colourless oil: ^{1}H NMR (300Hz, $CDCl_3$) 9.80(1H br s), 7.50(1H, s), 7.42(2H, t), 7.20(1H, m), 7.13(2H, m), 6.80(1H, s), 3.30(2H, t), 2.95(2H, t), 2.79(2H, t), 2.70(2H, t), 2.07(2H, quint.). The maleic acid salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 52.69, H 5.71, N 10.23%; $C_{18}H_{23}N_3O_6S$ requires: C 52.80, H 5.66, N 10.27%.

EXAMPLE 19

N-[2-(4(5)-Imidazoyl)ethyl]-2-naphthylmethanesulfonamide

The title compound was prepared according to the procedure for Example 17, using 2-naphthylmethanesulfonyl chloride (prepared essentially as Example 4 step a) as the substrate in step c. The product (R_f 0.27; 1:10:90 ammonia(880)/methanol/dichloromethane) of the four steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.75(1H br s), 7.89(4H, m), 7.51(4H, m), 7.17(1H, t), 6.79(1H, s), 4.46(2H, s), 3.17(2H, dd), 2.66(2H, m). The maleic acid salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 54.30, H 5.09, N 9.55%; $C_{20}H_{21}N_3O_6S.0.5H_2O$ requires: C 54.33, H 5.03, N 9.53%.

EXAMPLE 20

(E)-N-[2-(4(5)-Imidazoyl)ethyl]-2-phenylethenesulfonamide

The title compound was prepared according to the procedure for Example 17, using *trans*-β-styrenesulfonyl chloride as the substrate in step c. The product (R_f 0.13; 1:10:90 ammonia(880)/methanol/dichloromethane) of the four steps was obtained as a colourless foam: ^{1}H NMR (300Hz, $CDCl_3$) 7.56(1H, d), 7.42(6H, m), 6.84(1H, s), 6.73(1H, d), 3.36(2H, t), 2.86(2H, t). Found: C 54.41, H 5.49, N 14.69%; $C_{13}H_{15}N_3O_2S.0.5H_2O$ requires: C 54.53, H 5.63, N 14.67%.

EXAMPLE 21

N-[2-(4(5)-Imidazoyl)ethyl]-phenylmethanesulfonamide

The title compound was prepared according to the procedure for Example 9, using phenylmethanesulfonyl chloride as the substrate in step c. The product (R_f 0.27; 1:10:90 ammonia(880)/methanol/dichloromethane) of the four steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.50(1H, s), 7.31(5H, m), 7.20(1H, t), 6.80(1H, s), 4.27(2H, s), 3.13(2H, m), 2.63(2H, t). Found: C 54.39, H 5.73, N 15.60%; $C_{12}H_{15}N_3O_2S$ requires: C 54.32, H 5.70, N 15.84%.

EXAMPLE 22

N-[2-(4(5)-Imidazoyl)ethyl]-8-quinolinesulfonamide

The title compound was prepared according to the procedure for Example 17, using 8-quinolinesulfonyl chloride as the substrate in step c. The product (R_f 0.34; 1:10:90 ammonia(880)/methanol/dichloromethane) of the four steps was obtained as a colourless crystalline solid: ^{1}H NMR (300Hz, $CDCl_3$) 8.82(1H, dd), 8.42(1H, dd), 8.25(1H, dd), 8.05(1H, d), 7.64(1H, dd), 7.51(1H, dd), 7.38(1H, d), 6.66(1H, d), 3.17(2H, t), 2.74(2H, t). Found: C 55.33, H 4.81, N 18.47%; $C_{14}H_{14}N_4O_2S$ requires: C 55.61, H 4.67, N 18.53%.

EXAMPLE 23

N-[2-(4(5)-Imidazoyl)ethyl]-2-cyclohexylethanesulfonamide

The title compound was prepared according to the procedure for Example 17, using 2-cyclohexylethanesulfonyl chloride (prepared essentially as Example 4 step a) as the substrate in step c. The product (R_f 0.27; 1:10:90 ammonia(880)/methanol/dichloromethane) of the four steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.80(1H br s), 7.51(1H, s), 7.05(1H, t), 6.81(1H, s), 3.13(2H, dd), 2.90(2H, m), 2.65(2H, t), 1.62(5H, m), 1.47(2H, m), 1.16(4H, m), 0.86(2H, m). Found: C 54.68, H 8.20, N 14.71%; $C_{13}H_{23}N_3O_2S$ requires: C 54.70, H 8.12, N 14.72%.

EXAMPLE 24

N-[2-(4(5)-Imidazoyl)ethyl]-(3,4-dichlorophenyl)methanesulfonamide

The title compound was prepared according to the procedure for Example 9, using (3,4-dichlorophenyl)methanesulfonyl chloride (prepared essentially as Example 4 step a) as the substrate in step a. The product (R_f 0.31; 1:10:90 ammonia(880)/methanol/dichloromethane) of the four steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.85(1H br s), 7.60(3H, m), 7.32(1H, dd), 7.23(1H, t), 6.82(1H, s), 4.36(2H, s), 3.16(2H, dd), 2.65(2H, t). Found: C 42.79, H 3.98, N 12.49%; $C_{12}H_{13}Cl_2N_3O_2S$ requires: C 43.12, H 3.92, N 12.57%.

EXAMPLE 25

N-[2-(4(5)-Imidazoyl)ethyl]-(4-chlorophenyl)methanesulfonamide

The title compound was prepared according to the procedure for Example 9, using (4-chlorophenyl)methanesulfonyl chloride (prepared essentially as Example 4 step a) as the substrate in step a. The product (R_f 0.19; 1:10:90 ammonia(880)/methanol/dichloromethane) of the four steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.54(1H, d), 7.43(2H, d), 7.34(2H, d), 7.16(1H, t), 6.82(1H, s), 4.31(2H, s), 3.14(2H, dd), 2.65(2H, t). Found: C 48.01, H 4.80, N 14.14%; $C_{12}H_{14}ClN_3O_2S$ requires: C 48.08, H 4.71, N 14.02%.

EXAMPLE 26

N-[3-(4(5)-Imidazoyl)propyl]-(4-chlorophenyl)methanesulfonamide

Step a. *N-[3-(1-(triphenylmethyl)imidazoyl-4-yl)propyl]-(4-chlorophenyl)methanesulfonamide.* 4-(3-Aminopropyl)-1-(triphenylmethyl)-imidazole (Example 14 step b) (593mg, 1.61mmol) was reacted with (4-chlorophenyl)methanesulfonyl chloride (prepared essentially as Example 4 step a) (545mg, 2.42mmol) in the presence of triethylamine (270μl, 1.94mmol) according to the procedure of step a Example 9. Thus, the product was isolated as a colourless foam (489mg, 62%).

Step b. The product from step a was deprotected according to the procedure of step d Example 17 and the title compound (R_f 0.17; 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated in quantative yield as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.77(1H, br s), 7.50(1H, s), 7.43(2H, d), 7.37(2H, d), 7.14(1H, t), 6.72(1H, s), 4.32(2H, s), 2.92(2H, dd), 2.46(2H, t), 1.70(2H, m). Found: C 49.54, H 5.38, N 13.12%; $C_{13}H_{16}ClN_3O_2S$ requires: C 49.76, H 5.14, N 13.39%.

EXAMPLE 27

N-*[3-(4(5)-Imidazoyl)propyl]-benzenesulfonamide*

The title compound was prepared according to the procedure for Example 26, using benzenesulfonyl chloride as the substrate in step a. The product (R_f 0.16; 1:10:90 ammonia(880)/methanol/dichloromethane) of the four steps was obtained as a white solid: ^{1}H NMR (300Hz, $CDCl_3$) 7.86(2H, d), 7.54(4H, m), 6.76(1H, s), 3.04(2H, t), 2.67(2H, t), 1.81(2H, quint.). FAB M/S: [M^++H] 266; Accurate mass: 266.0936; $C_{12}H_{16}N_3O_2S$ requires: 266.0963. The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 28

N-*[3-(4(5)-Imidazoyl)propyl]-2-naphthalenesulfonamide*

The title compound was prepared according to the procedure for Example 26, using 2-naphthalenesulfonyl chloride as the substrate in step a. The product (R_f 0.17; 1:10:90 ammonia(880)/methanol/dichloromethane) of the four steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 8.40(1H, s), 8.10(2H, t), 8.02(1H, d), 7.74(4H, m), 7.44(1H, s), 6.62(1H, s), 2.78(2H, dd), 2.43(2H, t), 1.62(2H, quint.). Found: C 60.69, H 5.51, N 13.18%; $C_{16}H_{17}N_3O_2S$ requires: C 60.93, H 5.43 N 13.32%.

EXAMPLE 29

N-*[7-(4(5)-Imidazoyl)heptyl]-2-naphthalenesulfonamide*

Step a. *2-(*tert-*Butyldimethylsilyl)-1-(*N,N-*dimethylsulfamoyl)-imidazole.* A solution of 1-(*N,N*-dimethylsulfamoyl)-imidazole[1] (4.48g, 25.6mmol) in dry tetrahydrofuran (100ml) was cooled under an atmosphere of argon to -78°C. *n*-Butyl lithium (1.5M in hexanes) (18.0ml, 27.0mmol) was added over 30min and the solution stirred for a further 30min. To the resulting brown solution was added over 15min a solution of *tert*-butyldimethylsilyl chloride in dry tetrahydrofuran (20ml). The solution was allowed to warm to room temperature and stirred for 24h. Saturated ammonium chloride solution (100ml) and diethyl ether (100ml) were added and the ethereal extract was washed with brine and dried over magnesium sulfate. Filtration and evaporation of the filtrate gave an oily residue, which was purified by flash column chromatography (silica; ethyl acetate) to afford the product as an amber solid (6.97g, 94%).

Step b. *5-(7-Bromoheptyl)-2-(*tert-*butyldimethylsilyl)-1-(*N,N-*dimethylsulfamoyl) imidazole.* A solution of the product from step a (2.50g, 8.64mmol) in dry tetrahydrofuran (30ml) was cooled under an atmosphere of argon to -78°C. *n*-Butyl lithium (1.5M in hexanes) (8.50ml, 12.7mmol) was added over 15min and the solution stirred for a further 30min. A solution of 1,7-dibromoheptane (4.60g, 17.3mmol) in dry tetrahydrofuran (6ml) was added over 10min. The solution was stirred for 30min, allowed to warm to room temperature and stirred for 18h. Saturated ammonium chloride solution (50ml) and ethyl acetate (50ml) were added and the organic extract was washed with brine and dried over sodium sulfate. Filtration, evaporation of the filtrate and purification by flash column chromatography (silica; 20% ethyl acetate/hexane) afforded the product (R_f 0.55) as a white solid (2.48g, 62%).

Step c. *1-(*N,N-*Dimethylsulfamoyl)-5-(7-phthalimidoheptyl)-imidazole.* Potassium phthalimide (1.67g, 9.00mmol) was added to a solution of the product from step b (2.10g, 4.50mmol) in dry *N,N*-dimethylformamide (10ml), under an atmosphere of argon. The mixture was stirred and heated at 100°C for 18h and allowed to cool to room temperature. Water (75ml) was added and the mixture extracted with dichloromethane (3x40ml). The combined extracts were evaporated, the residue dissolved in ethyl acetate (75ml) and the solution washed five times with brine. The

solvent was evaporated and the residue purified by flash column chromatography (silica; ethyl acetate), from which the product was isolated as a yellow oil (1.75g, 93%).

Step d. *5-(7-Aminoheptyl)-1-(*N,N-*dimethylsulfamoyl)-imidazole*. The product from step c was deprotected according to the procedure of Example 17 step b.

Step e. The title compound was prepared according to the procedure for Example 6, using 5-(7-aminoheptyl)-1-(*N,N*-dimethylsulfamoyl)-imidazoleas the substrate in step a. The product (R_f 0.38; 1:10:90 ammonia(880)/methanol/dichloromethane) of the two steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 8.41 (1H, s), 8.13(2H, dd), 8.02(1H, dd), 7.80(1H, dd), 7.67(3H, m), 7.45(1H, d), 6.64(1H, s), 2.75(2H, dd), 2.38(2H, t), 1.43(2H, m), 1.32(2H, m), 1.13(6H, m).

EXAMPLE 30

N-*[8-(4(5)-Imidazoyl)octyl]-2-naphthalenesulfonamide*

The title compound was prepared according to the procedure for Example 6, using 5-(8-aminooctyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a. The product (R_f 0.39; 1:10:90 ammonia(880)/methanol/dichloromethane) of the two steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.72(1H, br s), 8.40 (1H, d), 8.13(2H, dd), 8.02(1H, dd), 7.80(1H, dd), 7.65(3H, m), 7.45(1H, d), 6.65(1H, d), 2.75(2H, dd), 2.41(2H, t), 1.45(2H, quint.), 1.32(2H, quint.), 1.12(8H, m).

EXAMPLE 31

N-*[10-(4(5)-Imidazoyl)decyl]-2-naphthalenesulfonamide*

The title compound was prepared according to the procedure for Example 6, using 5-(10-aminodecyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a. The product (R_f 0.33; 1:10:90 ammonia(880)/methanol/dichloromethane) of the two steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 8.40 (1H, d), 8.12(2H,

dd), 8.02(1H, dd), 7.80(1H, dd), 7.66(3H, m), 7.46(1H, d), 6.66(1H, s), 2.75(2H, dd), 2.44(2H, t), 1.47(2H, m), 1.31(2H, m), 1.10(12H, m).

EXAMPLE 32

N-[7-(4(5)-Imidazoyl)heptyl]-(4-chlorophenyl)methanesulfonamide

The title compound was prepared according to the procedure for Example 9, using 5-(7-aminoheptyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole (Example 29 step d) as the substrate in step a. The product (R_f 0.30; 1:10:90 ammonia(880)/methanol/dichloromethane) of the two steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.56(1H, s), 7.42(2H, d), 7.37(2H, d), 7.04(1H, t), 6.72(1H, s), 4.30(2H, s), 2.85(2H, dd), 2.48(2H, m), 1.53(2H, m), 1.37(2H, m), 1.24(6H, m).

EXAMPLE 33

N-[8-(4(5)-Imidazoyl)octyl]-(4-chlorophenyl)methanesulfonamide

Step a. *5-(8-Bromooctyl)-2-(*tert*-butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl) imidazole.* A solution of 2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl) imidazole (Example 29 step a) (2.62g, 9.05mmol) in dry tetrahydrofuran (30ml) was cooled under an atmosphere of argon to -78°C. *n*-Butyl lithium (1.5M in hexanes) (7.25ml, 10.9mmol) was added over 15min and the solution stirred for a further 30min. A solution of 1,8-dibromooctane (2.55ml 13.6mmol) in dry tetrahydrofuran (5ml) was added over 10min. The solution was stirred for 2h, allowed to warm to room temperature and stirred for 18h. Saturated ammonium chloride solution (30ml) and diethyl ether (30ml) were added and the ethereal extract was washed with brine and dried over sodium sulfate. Filtration, evaporation of the filtrate and purification by flash column chromatography (silica; 20% ethyl acetate/hexane) to afford the product (R_f 0.43) as a white solid (2.36g, 54%).

Step b. *2-(*tert*-Butyldimethylsilyl)-1-(N,N-dimethylsulfamoyl)-5-(8-phthalimidooctyl) imidazole (A) and 1-(N,N-dimethylsulfamoyl)-5-(8-phthalimidooctyl)-imidazole (B).*

Potassium phthalimide (1.84g, 9.95mmol) was added to a solution of the product of step a (2.39g, 4.97mmol) in dry dimethyl formamide (16ml), under an atmosphere of argon. The mixture was stirred and heated at 100°C for 18h and allowed to cool to room temperature. Water (80ml) was added and the mixture extracted with dichloromethane (3x40ml). The combined extracts were evaporated, the residue dissolved in ethyl acetate (80ml) and the solution washed four times with brine. The solvent was evaporated and the residue purified by flash column chromatography (silica; ethyl acetate), from which compound (**A**) (R_f 0.72) was isolated as an amber oil (639mg, 23%) and compound (**B**) (R_f 0.27) as an oily solid (1.56g, 73%).

Step c. *5-(8-Aminooctyl)-2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl) imidazole.* Compound A from step b was deprotected according to the procedure of Example 17 step b.

Step d. The title compound was prepared according to the procedure for Example 9, using 5-(8-aminooctyl)-2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole, the product of the previous reaction, as the substrate in step a. The product (R_f 0.42; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.47(1H, d), 7.43(2H, d), 7.36(2H, d), 7.03(1H, t), 6.68(1H, s), 4.30(2H, s), 2.85(2H, dd), 2.46(2H, t), 1.53(2H, m), 1.37(2H, m), 1.23(8H, m). Found C 55.99, H 7.04, N 10.67%. $C_{18}H_{26}ClN_3O_2S$ requires C 56.31, H 6.83, N 10.94%

EXAMPLE 34

N-[10-(4(5)-Imidazoyl)decyl]-(4-chlorophenyl)methanesulfonamide

The title compound was prepared according to the procedure for Example 9, using 5-(10-aminodecyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a. The product (R_f 0.37; 1:10:90 ammonia(880)/methanol/dichloromethane) of the two steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.46(1H, d), 7.43(2H, dd), 7.37(2H, d), 7.04(1H, t), 6.67(1H, s), 4.31(2H, s), 2.85(2H, dd), 2.45(2H, t), 1.53(2H, m), 1.37(2H, m), 1.21(12H, m).

EXAMPLE 35

N-[2-(4(5)-Imidazoyl)ethyl]-N'-phenylmethyl-sulfamide

4-(2-Aminoethyl)-1-(triphenylmethyl)-imidazole (Example 17 step b) was converted to *N*-2-[1-(triphenylmethyl)imidazol-4-yl]ethyl-*N'-tert*-butoxycarbonyl-sulfamide according to the procedure of Example 12 step a. The subsequent alkylation with benzyl bromide was performed essentially as Example 12 step b and gave *N*-[2-(1-(triphenylmethyl)imidazol-4-yl)ethyl]-*N'-tert*-butoxycarbonyl-*N'*-phenylmethyl-sulfamide. The final deprotection was carried out in the manner of Example 17 step b and the title compound (R_f 0.21; 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a colourless oil: ^{1}H NMR (300Hz, d_6-DMSO) 7.50(1H, s), 7.30(6H, m), 6.95(1H, t), 6.78(1H, s), 3.96(2H, s), 3.03(2H, dd), 2.65(2H, t). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 48.05, H 5.10, N 13.87%; $C_{16}H_{20}N_4O_6S$ requires: C 48.48, H 5.09 N 14.13%.

EXAMPLE 36

N-[3-(4(5)-Imidazoyl)propyl]-N'-phenylmethyl-sulfamide

The title compound was prepared according to the procedure for Example 35, using 4-(3-aminopropyl)-1-(triphenylmethyl)-imidazole (Example 14 step b) as the initial substrate, and was isolated as a white solid (R_f 0.10; 1:10:90 ammonia(880)/methanol/dichloromethane): ^{1}H NMR (300Hz, d_6-DMSO) 11.75(1H, br s), 7.49(1H, s), 7.30(5H, m), 7.25(1H, m), 6.96(1H, t), 6.71(1H, s), 3.98(2H, s), 2.82(2H, m), 2.48(2H, m), 1.72(2H, m). Found: C 53.03, H 6.19, N 18.89%; $C_{13}H_{18}N_4O_2S$ requires: C 53.04, H 6.16, N 19.03%.

EXAMPLE 37

N-[2-(4(5)-Imidazoyl)ethyl]-N'-(4-chlorophenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 35, using 4-chlorobenzyl bromide in the alkylation step, and was isolated as a white solid (R_f

0.20; 1:10:90 ammonia(880)/methanol/dichloromethane): ^{1}H NMR (300Hz, d_6-DMSO) 11.75(1H, br s), 7.51(1H, s), 7.36(5H, m), 6.99(1H, t), 6.75(1H, s), 3.96(2H, s), 3.01(2H, dd), 2.65(2H, t). Found: C 45.47, H 4.83, N 17.93%; $C_{12}H_{15}ClN_4O_2S$ requires: C 45.79 H 4.80, N 17.80%.

EXAMPLE 38

N-[7-(4(5)-Imidazoyl)heptyl]-N'-(4-chlorophenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(7-aminoheptyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole (Example 29 step d) as the substrate in step a. The product (R_f 0.28; 1:10:90 ammonia(880)/methanol/dichloromethane) of the three steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.45(1H, s), 7.36(5H, m), 6.84(1H, t), 6.67(1H, s), 3.98(2H, s), 2.79(2H, dd), 2.46(2H, t), 1.53(2H, m), 1.37(2H, m), 1.23(6H, m). Found C 53.17, H 6.62, N 14.53%. $C_{17}H_{25}ClN_4O_2S$ requires C 53.05, H 6.55, N 14.56%

EXAMPLE 39

N-[8-(4(5)-Imidazoyl)octyl]-N'-(4-chlorophenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(8-aminooctyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a. The product (R_f 0.30; 1:10:90 ammonia(880)/methanol/dichloromethane) of the three steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.45(1H, s), 7.36(5H, m), 6.82(1H, t), 6.67(1H, s), 3.98(2H, d), 2.74(2H, dd), 2.45(2H, t), 1.55(2H, m), 1.37(2H, m), 1.23(8H, m).

EXAMPLE 40

N-[10-(4(5)-Imidazoyl)decyl]-N'-(4-chlorophenyl)methyl-sulfamide

5-(10-Aminodecyl)-2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole was prepared according to the procedure of Example 33 steps a, b and c, using 1,10-

dibromodecane as the alkylating reagent in step a. This amine was converted to the title compound according to the procedure of Example 12. The product (R_f 0.41; 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.45(1H, s), 7.35(5H, m), 6.82(1H, t), 6.66(1H, s), 3.98(2H, d), 2.74(2H, dd), 2.45(2H, t), 1.53(2H, m), 1.37(2H, m), 1.21(12H, m). Found C 55.97, H 7.55, N 12.88%. $C_{20}H_{31}ClN_4O_2S$ requires C 56.26, H 7.32, N 13.12%

EXAMPLE 41

N-[4-(4(5)-Imidazoyl)butyl]-N'-(3,4-dichlorophenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(4-aminobutyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 3,4-dichlorobenzyl bromide in step b. The product (R_f 0.26; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, $CDCl_3$) 7.51(1H, d), 7.42(2H, m), 7.19(1H, dd), 6.76(1H, d), 4.17(2H, s), 3.06(2H, t), 2.62(2H, t), 1.68(2H, quint.), 1.59(2H, quint.). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 42

N-[4-(4(5)-Imidazoyl)butyl]-N'-(3-chlorophenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(4-aminobutyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 3-chlorobenzyl bromide in step b. The product (R_f 0.26; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.73(1H, br s), 7.47(1H, d), 7.35(5H, m), 6.88(1H, t), 6.69(1H, s), 4.00(2H, d), 2.79(2H, dd), 2.45(2H, t), 1.55(2H, m), 1.42(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 43

N-[4-(4(5)-Imidazoyl)butyl]-N'-(2-chlorophenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(4-aminobutyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 2-chlorobenzyl bromide in step b. The product (R_f 0.26; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.75(1H, br s), 7.53(1H, d), 7.47(1H, s), 7.35(4H, m), 6.95(1H, t), 6.68(1H, s), 4.09(2H, d), 2.83(2H, dd), 2.45(2H, t), 1.55(2H, m), 1.46(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 44

N-[4-(4(5)-Imidazoyl)butyl]-N'-(4-iodophenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(4-aminobutyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 4-iodobenzyl bromide in step b. The product (R_f 0.24; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.75(1H, br s), 7.67(2H, d), 7.49(1H, s), 7.33(1H, t), 7.14(2H, d), 6.85(1H, t), 6.70(1H, s), 3.94(2H, d), 2.79(2H, dd), 2.46(2H, t), 1.55(2H, m), 1.46(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 45

N-[4-(4(5)-Imidazoyl)butyl]-N'-(4-bromophenyl)methyl-sulfamide

Step a. *N-[4-(1-(N'',N''-Dimethylsulfamoyl)imidazol-4-yl)butyl]-N'-tert-butoxycarbonyl-sulfamide*. 5-(4-Aminobutyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] was converted to the product according to the procedure of Example 12 step a.

Step b. *N-[4-(1-(N'',N''-Dimethylsulfamoyl)imidazol-4-yl)butyl]-N'-(4-*

bromophenyl)methyl-N'-tert-*butoxycarbonyl-sulfamide (A)*. The product from step a (500mg, 1.27mmol) was allowed to react with 4-bromobenzyl bromide in the manner of Example 12 step b. The crude product mixture was purified by flash column chromatography (silica; 50% ethyl acetate/dichloromethane) and gave the product (**A**) (R_f 0.37) as a yellow oil (267mg, 35%) and *N,N'*-di-[(4-bromophenyl)methyl]-*N*-[4-(1-(*N''*,*N''*-dimethylsulfamoyl)imidazol-4-yl)butyl]-*N'-tert*-butoxycarbonyl-sulfamide (**B**) (R_f 0.56) (220mg, 23%).

Step c. The product (**A**) from step b was deprotected according to the procedure of Example 12 step c and the title compound (R_f 0.28; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.50(3H, m), 7.35(1H, t), 7.28(2H, d), 6.87(1H, t), 6.71(1H, s), 3.96(2H, d), 2.78(2H, dd), 2.46(2H, t), 1.55(2H, m), 1.42(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 40.66, H 4.90, N 10.67%; $C_{18}H_{23}BrN_4O_6S.1.5H_2O$ requires: C 40.76, H 4.94, N 10.56%.

EXAMPLE 46

N-*[4-(4(5)-Imidazoyl)butyl]*-N'-*(4-fluorophenyl)methyl-sulfamide*

The title compound was prepared according to the procedure for Example 12, using 5-(4-aminobutyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 4-fluorobenzyl bromide in step b. The product (R_f 0.26; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.67(1H, br s), 7.46(1H, s), 7.35(3H, m), 7.14(2H, m), 6.85(1H, t), 6.68(1H, s), 3.97(2H, d), 2.79(2H, dd), 2.46(2H, m), 1.54(2H, m), 1.45(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 44.92, H 5.61, N 11.42%; $C_{18}H_{23}FN_4O_6S.2.0H_2O$ requires: C 45.18, H 5.69, N 11.71%.

EXAMPLE 47

N-*[4-(4(5)-Imidazoyl)butyl]*-N'-*(4-(trifluoromethyl)phenyl)methyl-sulfamide*

The title compound was prepared according to the procedure for Example 12, using 5-(4-aminobutyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 4-(trifluoromethyl)benzyl bromide in step b. The product (R_f 0.26; 1:10:90 ammonia(880)/methanol/dichloromethane) of the three steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.70(1H, br s), 7.68(2H, d), 7.54(2H, d), 7.44(2H, m), 6.90(1H, t), 6.68(1H, s), 4.09(2H, d), 2.80(2H, dd), 2.45(2H, t), 1.55(2H, m), 1.45(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 43.17, H 4.99, N 10.88%; $C_{19}H_{23}F_3N_4O_6S.2.0H_2O$ requires: C 43.18, H 5.15, N 10.60%.

EXAMPLE 48

N-[4-(4(5)-Imidazoyl)butyl]-N'-(4-methoxyphenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(4-aminobutyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 4-methoxybenzyl bromide in step b. The product (R_f 0.26; 1:10:90 ammonia(880)/ methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.70(1H, br s), 7.47(1H, s), 7.22(2H, d), 7.18(1H, t), 6.87(2H, d), 6.79(1H, t), 6.68(1H, s), 3.90(2H, d), 3.72(3H, s), 2.79(2H, dd), 2.45(2H, t), 1.55(2H, m), 1.44(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 50.19, H 5.80, N 12.36%; $C_{19}H_{26}N_4O_7S$ requires: C 50.21, H 5.77, N 12.33%.

EXAMPLE 49

N-[4-(4(5)-Imidazoyl)butyl]-N'-(4-biphenyl)methyl-sulfamide

5-(4-Aminobutyl)-2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole was isolated as a by-product during the preparation of 5-(4-aminobutyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole,[1] in analogous fashion to Example 33. It was converted to the title compound using the procedure for Example 12, using (4-chloromethyl)biphenyl as the substrate in step b. Step b was further modified by heating the reaction mixture at 50°C for 2h prior to work up. The product (R_f 0.28;

1:10:90 ammonia(880)/ methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.75(1H, br s), 7.63(4H, m), 7.42(5H, m), 7.33(2H, m), 6.86(1H, t), 6.69(1H, s), 4.03(2H, d), 2.82(2H, dd), 2.46(2H, t), 1.54(2H, m), 1.45(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 54.71, H 5.87, N 10.80%; $C_{24}H_{28}N_4O_6S.1.5H_2O$ requires: C 54.63, H 5.92, N 10.61%.

EXAMPLE 50

N-[4-(4(5)-Imidazoyl)butyl]-N'-2-naphthylmethyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(4-aminobutyl)-2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole (Example 49) as the substrate in step a and 2-bromomethyl-naphthalene in step b. The product (R_f 0.24; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.70(1H, br s), 7.85(4H, m), 7.48(4H, m), 7.40(1H, t), 6.88(1H, t), 6.71 and 6.58 (1H, 2x br s), 4.16(2H, d), 2.83(2H, dd), 2.43(2H, m), 1.53(2H, m), 1.45(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 55.49, H 5.66, N 11.59%; $C_{22}H_{26}N_4O_6S$ requires: C 55.68, H 5.52, N 11.81%.

EXAMPLE 51

N-[4-(4(5)-Imidazoyl)butyl]-N'-cyclohexylmethyl-sulfamide

Step a. *(Z)-4-[4-(1,3-Dioxolan-2-yl)but-2-enyl]-1-(triphenylmethyl)-imidazole.* A suspension of [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide (48.54g, 109mmol) in dry tetrahydrofuran (500ml) was cooled, under an atmosphere of argon, to -20°C. *n*-Butyl lithium (1.6M in hexanes) (68.3ml, 109mmol) was added dropwise and the solution stirred for a 1h. A solution of [1-(triphenylmethyl)imidazol-4-yl]carbaldehyde[4] (36.80g, 109mmol) in dry tetrahydrofuran (500ml) was added slowly dropwise and the reaction mixture stirred at room temperture for 18h. The reaction mixture was concentrated *in vacuo*, water was added and the mixture filtered through

a pad of Celite. The filtrate was extracted with dichloromethane (2x500ml) and the combined extracts dried over magnesium sulfate. Filtration and evaporation gave a yellow oil. From flash column chromatography (silica; 10-20% ethyl acetate/hexane) the product was isolated as a yellow oil (19.73g, 42%).

Step b. *4-[4-(1,3-Dioxolan-2-yl)butyl]-1-(triphenylmethyl)-imidazole.* A solution of the product from step a in ethanol was hydrogenated in the presence of a catalytic quantity of 10% palladium-on-charcoal at atmospheric pressure and temperature for 18h. The product was isolated as a colourless oil in quantitative yield.

Step c. *4-[1-(Triphenylmethyl)imidazol-4-yl]butan-1-al.* A suspension of the product from step b (19.8g, 46.6mmol) in a mixture of acetone (300ml) and 2M hydrochloric acid (50ml) was stirred at room temperature for 20h. The mixture was neutralised with sodium hydrogen carbonate, filtered and the filtrate extracted with dichloromethane (3x100ml). The combined extracts were dried over magnesium sulfate, filtered and evaporated to give the product as a colourless oil (16.1g, 91%).

Step d. *4-[1-(Triphenylmethyl)imidazol-4-yl]butan-1-ol.* A solution of the product from step c (16.1g, 42.4mmol) in ethanol (300ml) was cooled under an atmosphere of argon to 0°C. Sodium borohydride (1.57g, 42.4mmol) was added, the mixure stirred for 4h and carefully quenched with saturated ammonium chloride. The mixture was extracted with dichloromethane (3x100ml). The combined extracts were dried over magnesium sulfate, filtered and evaporated to give a white solid, which was dissolved in a 5% methanol/dichloromethane and preciptated with diethyl ether. Thus, the product was isolated as a colourless crystalline solid (9.34g, 58%).

Step e. N-tert-*Butoxycarbonyl*-N'-*cyclohexylmethyl-sulfamide.* Cyclohexylmethylamine was converted to the product using essentially the procedure described in step a of Example 12.

Step f. N-tert-*Butoxycarbonyl*-N-*[4-[1-(triphenylmethyl)imidazol-4-yl]butyl]*-N'-

cyclohexylmethyl-sulfamide. To a solution of the product from step d (764mg, 2.00mmol), the product from step e (642mg, 2.20mmol) and triphenylphosphine (576mg, 2.20mmol) in dry tetrahydrofuran (20ml), under an atmosphere of argon, was added over 10min a solution of diethylazodicarboxylate (383mg, 2.20mmol) in dry tetrahydrofuran (5ml). The mixture was stirred for 2h, the solvent evaporated and the residue purified by flash column chromatography (silica; 30% ethyl acetate/dichloromethane). Thus, the product was isolated as a colourless foam (800mg, 60%).

Step g. A solution of the product of step f (800mg, 1.20mmol) in a mixture of ethanol (15ml) and 2M hydrochloric acid (5ml) was heated at reflux for 2h. The solvent was evaporated and the residue purified by flash column chromatography (silica; 1:10:90 ammonia(880)/ methanol/dichloromethane). Thus, the title compound (R_f 0.28) was isolated as a white solid (184mg, 49%). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan: ^{1}H NMR (300Hz, d_6-DMSO) 8.87(1H, s), 7.36(1H, s), 6.70(1H, t), 6.02(1H, s), 2.80(2H, dd), 2.61(4H, m), 1.63(7H, m), 1.44(3H, m), 1.13(3H, m), 0.83(2H, m).

EXAMPLE 52

N-[4-(4(5)-Imidazoyl)butyl]-N'-adamant-1-ylmethyl-sulfamide

The title compound was prepared according to the procedure for Example 51, using 1-adamant-1-ylmethylamine as the substrate in step e. The product (R_f 0.32; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.66(1H, br s), 7.45(1H, s), 6.70(1H, br s), 6.66(1H, t), 6.57(1H, t), 2.78(2H, m), 2.48(4H, m), 1.91(3H, s), 1.56(8H, m), 1.44(8H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 53

N-[3-(4(5)-Imidazoyl)propyl]-2-(4-chlorophenyl)ethanesulfonamide

Step a. *N-[3-(1-(triphenylmethyl)imidazoyl-4-yl)propyl]-2-(4-chlorophenyl)ethanesulfonamide.* 4-(3-Aminopropyl)-1-(triphenylmethyl)-imidazole (Example 14 step b) (500mg, 1.01mmol) and 2-(4-chlorophenyl)ethanesulfonyl chloride (prepared essentially as Example 4 step a) (266mg, 1.01mmol) were reacted together in the presence of triethylamine (155μl, 1.94mmol) according to the procedure of Example 9 step a. The product was isolated as a colourless foam (494mg, 86%).

Step b. The product from step a (494mg, 0.87mmol) was deprotected according to the procedure of Example 17 step d and the title compound was isolated as a white solid (154mg, 54%): ^{1}H NMR (300Hz, d_4-MeOH) 7.66(1H, s), 7.38(2H, d), 7.63(2H, d), 6.90(1H, s), 3.37(2H, m), 3.14(4H, m), 2.74(2H, t), 1.94(2H, quint.). Found C 51.25, H 5.61, N 12.72%. $C_{14}H_{18}ClN_3O_2S$ requires C 51.29, H 5.53, N 12.82%

EXAMPLE 54

N-*[5-(4(5)-Imidazoyl)pentyl]-2-(4-chlorophenyl)ethanesulfonamide*

Step a. N-*[5-(2-(*tert-*Butyldimethylsilyl)-1-(*N',N'-*dimethylsulfamoyl)imidazol-4-yl)pentyl]-2-(4-chlorophenyl)ethanesulfonamide.* 5-(5-Aminopentyl)-2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole was isolated as a by-product during the preparation of 5-(5-aminopentyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole,[1] in analogous fashion to Example 33. It was allowed to react with 2-(4-chlorophenyl)ethanesulfonyl chloride (prepared essentially as Example 4 step a) in the manner of Example 9 step a. The product was obtained as a yellow oil.

Step b. The product from step a (494mg, 0.87mmol) was deprotected according to the procedure of Example 12 step c and the title compound was isolated as a white solid (227mg, 92%): ^{1}H NMR (300Hz, d_4-MeOH) 7.58(1H, s), 7.34(2H, d), 7.29(2H, d), 6.80(1H, s), 3.31(2H, m), 3.09(4H, m), 2.63(2H, m), 1.70(2H, m), 1.60(2H, m), 1.44(2H, m). Found C 54.04, H 6.27, N 11.55%. $C_{16}H_{22}ClN_3O_2S$ requires C 54.00, H 6.23, N 11.83%

EXAMPLE 55

N-[4-(4(5)-Imidazoyl)butyl]-2-(4-chlorophenyl)ethanesulfonamide

The title compound was prepared according to the procedure for Example 54, using 5-(4-aminobutyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] as the amine component in step a. The product was obtained as a white solid: ^{1}H NMR (300Hz, $CDCl_3$) 7.56(1H, s), 7.30(2H, dd), 7.16(2H, d), 6.78(1H, s), 4.55 (1h br s), 3.25(2H, m), 3.09(4H, m), 2.64(2H, t), 1.72(2H, quint.), 1.58(2H, quint.). Found C 52.52, H 5.92, N 12.11%. $C_{15}H_{20}ClN_3O_2S$ requires C 51.70, H 5.90, N 12.29%

EXAMPLE 56

N-[3-(4(5)-Imidazoyl)propyl]-N'-2-(4-chlorophenyl)ethyl-sulfamide

Step a. N-tert-*Butoxycarbonyl*-N'-*2-(4-chlorophenyl)ethyl-sulfamide.* 2-(4-chlorophenyl)ethylamine was converted to the product using essentially the procedure described in step a of Example 12.

Step b. N-tert-*Butoxycarbonyl*-N-*[3-[1-(triphenylmethyl)imidazol-4-yl]propyl]*-N'-*2-(4-chlorophenyl)ethyl-sulfamide.* The product from step a and 3-[1-(triphenylmethyl)imidazol-4-yl]propan-1-ol[3] were allowed to react together under the conditions of Example 51 step f. The product was isolated as a white foam.

Step c. The product from step b was deprotected according to the procedure of Example 12 step c and the title compound was isolated as a white solid: ^{1}H NMR (300Hz, d_4-MeOH) 7.58(1H, s), 7.28(4H, m), 6.82(1H, s), 3.20(2H, t), 2.86(4H, m), 2.64(2H, t), 1.83(2H, quint.). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found C 46.87, H 5.14, N 12.36%. $C_{18}H_{23}ClN_4O_6S$ requires C 47.11, H 5.05, N 12.21%

EXAMPLE 57

N-[4-(4(5)-Imidazoyl)butyl]-N'-2-(4-chlorophenyl)ethyl-sulfamide

The title compound was prepared according to the procedure for Example 56, using 4-[1-(triphenylmethyl)imidazol-4-yl]butan-1-ol (Example 51 step d) in step b. The product was obtained as colourless oil: ^{1}H NMR (300Hz, d_4-MeOH) 7.53(1H, s), 7.24(4H, m), 6.75(1H, s), 3.15(2H, t), 2.83(4H, m), 2.57(2H, t), 1.57(4H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found C 48.28, H 5.44, N 11.62%. $C_{19}H_{25}ClN_4O_6S$ requires C 48.25, H 5.33, N 11.85%

EXAMPLE 58

N-[6-(4(5)-Imidazoyl)hexyl]-N'-(4-bromophenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(6-aminohexyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 4-bromobenzyl bromide in step b. The product was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.52(3H, m), 7.37(1H, t), 7.31(2H, d), 6.86(1H, t), 6.70(1H, s), 3.99(2H, d), 2.77(2H, dd), 2.48(2H, t), 1.55(2H, m), 1.41(2H, m), 1.28(4H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found C 44.92, H 5.17, N 10.58%. $C_{20}H_{27}BrN_4O_6S$ requires C 45.20, H 5.12, N 10.54%

EXAMPLE 59

N-[6-(4(5)-Imidazoyl)hexyl]-N'-(4-fluorophenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(6-aminohexyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 4-fluorobenzyl bromide in step b. The product was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.50(1H, br s), 7.48(1H, s), 7.35(3H, m), 7.16(2H, m), 6.86(1H, t), 6.70(1H, s), 4.00(2H, d), 2.78(2H, dd), 2.48(2H, t), 1.55(2H, m), 1.42(2H, m), 1.28(4H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found C 51.25, H 5.79, N 11.72%. $C_{20}H_{27}FN_4O_6S$ requires C 51.05, H 5.78, N 11.91%

EXAMPLE 60

N-[6-(4(5)-Imidazoyl)hexyl]-N'-(4-(trifluoromethyl)phenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(6-aminohexyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 4-(trifluoromethyl)benzyl bromide in step b. The product was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.70(1H, br s), 7.70(2H, d), 7.58(2H, d), 7.49(1H, s), 7.47(1H, s), 6.91(1H, t), 6.70(1H, s), 4.12(2H, d), 2.78(2H, dd), 2.48(2H, t), 1.54(2H, m), 1.41(2H, m), 1.27(4H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 61

N-[6-(4(5)-Imidazoyl)hexyl]-N'-(4-iodophenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(6-aminohexyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 4-iodobenzyl bromide in step b. The product was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.75(1H, br s), 7.67(2H, d), 7.45(1H, s), 7.33(1H, t), 7.14(2H, d), 6.82(1H, t), 6.67(1H, s), 3.94(2H, d), 2.74(2H, dd), 2.46(2H, t), 1.52(2H, m), 1.37(2H, m), 1.25(4H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found C 41.62, H 4.75, N 9.59%. $C_{20}H_{27}IN_4O_6S$ requires C 41.53, H 4.71, N 9.69%

EXAMPLE 62

N-[6-(4(5)-Imidazoyl)hexyl]-N'-(4-biphenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 49, using 5-(6-aminohexyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole.[1] The product was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.75(1H, br s), 7.62(4H, m), 7.42(5H, m), 7.33(2H, m), 6.83(1H, t), 6.66(1H, s), 4.03(2H, d), 2.78(2H, dd),

2.44(2H, t), 1.51(2H, m), 1.38(2H, m), 1.26(4H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 63

N-*[5-(4(5)-Imidazoyl)pentyl]*-N'-*(4-(trifluoromethyl)phenyl)methyl-sulfamide*

The title compound was prepared according to the procedure for Example 12, using 5-(5-aminopentyl)-2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole (Example 54 step a) as the substrate in step a and 4-(trifluoromethyl)benzyl bromide in step b. The product was obtained as a white crystalline solid: ^{1}H NMR (300Hz, d_4-MeOH) 7.62(2H, d), 7.56(3H, m), 6.75(1H, s), 4.40(2H, s), 2.92(2H, t), 2.57(2H, t), 1.63(2H, quint.), 1.55(2H, quint.), 1.38(2H, m).

EXAMPLE 64

N-*[5-(4(5)-Imidazoyl)pentyl]*-N'-*(4-bromophenyl)methyl-sulfamide*

The title compound was prepared according to the procedure for Example 12, using 5-(5-aminopentyl)-2-(*tert*-butyldimethylsilyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole (Example 54 step a) as the substrate in step a and 4-bromobenzyl bromide in step b. The product was obtained as a white crystalline solid: ^{1}H NMR (300Hz, d_4-MeOH) 7.53(1H, s), 7.47(2H, d), 7.28(2H, d), 6.75(1H, s), 4.08(2H, s), 2.90(2H, t), 2.57(2H, t), 1.63(2H, quint.), 1.50(2H, quint.), 1.38(2H, m).

EXAMPLE 65

N-*[5-(4(5)-Imidazoyl)pentyl]*-N'-*(4-fluorophenyl)methyl-sulfamide*

The title compound was prepared according to the procedure for Example 12, using 5-(5-aminopentyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 4-fluorobenzyl bromide in step b. The product was obtained as a white solid: ^{1}H NMR (300Hz, d_4-MeOH) 7.54(1H, s), 7.37(2H, dd), 7.04(2H, t), 6.75(1H, s), 4.09(2H, s), 2.90(2H, t), 2.50(2H, t), 1.64(2H, quint.), 1.52(2H, quint.), 1.37(2H,

m).

EXAMPLE 66

N-[5-(4(5)-Imidazoyl)pentyl]-N'-(4-iodophenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 12, using 5-(5-aminopentyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] as the substrate in step a and 4-iodobenzyl bromide in step b. The product was obtained as a white solid: ^{1}H NMR (300Hz, d_4-MeOH) 7.67(2H, d), 7.54(1H, s), 7.16(2H, d), 6.76(1H, s), 4.06(2H, s), 2.89(2H, t), 2.58(2H, t), 1.63(2H, quint.), 1.50(2H, quint.), 1.36(2H, m).

EXAMPLE 67

N,N'-Di-[(4-bromophenyl)methyl]-N-[4-(4(5)-imidazoyl)butyl]-sulfamide

N,N'-Di-[(4-bromophenyl)methyl]-*N*-[4-(1-(*N'',N''*-dimethylsulfamoyl)imidazol-4-yl)butyl]-*N'-tert*-butoxycarbonyl-sulfamide(Example 45, step b, product (**B**)) was deprotected according to the procedure of Example 12 step c and the title compound (R_f 0.45; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, $CDCl_3$) 7.43(5H, m), 7.16(4H, d), 6.68(1H, s), 4.27(2H, s), 4.12(2H, s), 3.13(2H, t), 2.53(2H, m), 1.53(4H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found C 44.62, H 4.29, N 8.35%. $C_{25}H_{28}Br_2N_4O_6S$ requires C 44.66, H 4.20, N 8.33%

EXAMPLE 68

N'-(4-Chlorophenyl)methyl-N,N'-dimethyl-N-[4-(4(5)-imidazoyl)butyl]-sulfamide

Step a. *N,N'-Dimethyl-N-[4-(1-(N'',N''-dimethylsulfamoyl)imidazol-4-yl)butyl]-N'-tert-butoxycarbonyl-sulfamide.* A solution of *N-[4-(1-(N'',N''*-dimethylsulfamoyl)imidazol-4-yl)butyl]-*N'-tert*-butoxycarbonyl-sulfamide(Example45 step a) (686mg, 1.67mmol) and iodomethane (218μl, 3.50mmol) in dry *N,N*-dimethylformamide (4ml) was cooled under an atmosphere of argon to 0°C. Sodium

hydride (147mg, 3.67mmol) was added and the reaction mixture was stirred and allowed to warm to room temperature overnight. The reaction was quenched with brine and extracted with ethyl acetate (2x50ml). The combined extracts were washed three times with water, dried over magnesium sulfate, filtered and evaporated to give a yellow oil. Flash column chromatography (silica; 0.5:5:95 ammonia(880)/methanol/dichloromethane) afforded the product as a colourless oil (356mg, 48%).

Step b. N,N'-*Dimethyl*-N-*[4-(1-(*N'',N''-*dimethylsulfamoyl)imidazol-4-yl)butyl]-sulfamide.* A solution of the product from step a (352mg, 0.80mmol) in trifluoroacetic acid (1ml) was stirred for 30min and the acid evaporated. The residue was dissolved in dichloromethane, neutralised with saturated sodium hydrogen carbonate solution and extracted with dichloromethane (3x10ml). The combined extracts were dried over magnesium sulfate, filtered and evaporated to give the product in quantitative yield as a colourless oil (271mg).

Step c. N'-*(4-Chlorophenyl)methyl*-N,N'-*dimethyl*-N-*[4-(1-(*N'',N''-*dimethylsulfamoyl)imidazol-4-yl)butyl]-sulfamide.* The product from step b (315mg, 0.93mmol) was alkylated with 4-chlorobenzyl bromide according to the procedure of Example 12 step b. Flash column chromatography (silica; 0.5:5:95 ammonia(880)/methanol/dichloromethane) afforded the product as a pale yellow oil (325mg, 75%).

Step d. The product from step c (325mg, 0.70mmol) was deprotected according to the procedure of Example 12 step c and the title compound was obtained as a white solid (81mg, 32%): ^{1}H NMR (300Hz, $CDCl_3$) 7.55(1H, d), 7.33(2H, dd), 7.26(2H, dd), 6.78(1H, s), 4.26(2H, s), 3.24(2H, t), 2.81(3H, s), 2.65(5H, m), 1.68(4H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found C 49.04, H 5.73, N 11.39%. $C_{20}H_{27}ClN_4O_6S$ requires C 49.33, H 5.59, N 11.51%

EXAMPLE 69

N'-*(4-Chlorophenyl)methyl*-N-*[4-(4(5)-imidazoyl)butyl]*-N-*methyl-sulfamide*

Step a. N'-*(4-Chlorophenyl)methyl*-N-*[4-(1-(*N'',N''-*dimethylsulfamoyl)imidazol-4-yl)butyl]*-N'-tert-*butoxycarbonyl-sulfamide.* 5-(4-Aminobutyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole[1] was converted to the product in analogous fashion to Example 12 steps a and b.

Step b. N'-*(4-Chlorophenyl)methyl*-N-*[4-(1-(*N'',N''-*dimethylsulfamoyl)imidazol-4-yl)butyl]*-N-*methyl*-N'-tert-*butoxycarbonyl-sulfamide.* The product from step a (310mg, 0.58mmol) was methylated according to the procedure of Example 68 step a. The product was obtained as a pale yellow oil (309mg, 97%).

Step c. The product from step b (325mg, 0.70mmol) was deprotected according to the procedure of Example 12 step c and the title compound was obtained as a white solid (80mg, 42%): ^{1}H NMR (300Hz, $CDCl_3$) 7.50(1H, s), 7.32(4H, m), 6.77(1H, s), 4.17(2H, s), 3.18(2H, t), 2.77(3H, s), 2.64(2H, t), 1.66(4H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found C 48.33, H 5.41, N 11.56%. $C_{19}H_{25}ClN_4O_6S$ requires C 48.25, H 5.33, N 11.85%

EXAMPLE 70

N'-*(4-Chlorophenyl)methyl*-N-*[4-(4(5)-imidazoyl)butyl]*-N'-*methyl-sulfamide*

Step a. N'-*(4-Chlorophenyl)methyl*-N-*[4-(1-(*N'',N''-*dimethylsulfamoyl)imidazol-4-yl)butyl]-sulfamide.* The *tert*-butoxycarbonyl group of *N'*-(4-chlorophenyl)methyl-*N*-[4-(1-(*N'',N''*-dimethylsulfamoyl)imidazol-4-yl)butyl]-*N'-tert*-butoxycarbonyl-sulfamide (Example 10) (414mg, 0.77mmol) was removed according to the procedure of Example 68 step b. The product was obtained as a white solid (290mg, 86%).

Step b. N'-*(4-Chlorophenyl)methyl*-N-*[4-(1-(*N'',N''-*dimethylsulfamoyl)imidazol-4-yl)butyl]*-N'-*methyl-sulfamide.* The product from step a (290mg, 0.66mmol) was methylated according to the procedure of Example 68 step a, using iodomethane

(43μl, 0.69mmol) and sodium hydride (28mg, 0.70mmol). The product was obtained as a colourless oil (49mg, 17%).

Step c. The product from step b (49mg, 0.11mmol) was deprotected according to the procedure of Example 12 step c and the title compound was obtained as a colourless oil (22mg, 58%): ^{1}H NMR (300Hz, $CDCl_3$) 7.56(1H, s), 7.32(2H, dd), 7.26(2H, dd), 6.76(1H, s), 4.26(2H, s), 3.09(2H, t), 2.68(3H, s), 2.64(2H, t), 1.71(2H, m), 1.61(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found C 48.36, H 5.52, N 11.61%. $C_{19}H_{25}ClN_4O_6S$ requires C 48.25, H 5.33, N 11.85%

EXAMPLE 71

(R)-(+)-N-[2-(4(5)-Imidazoyl)-1-methyl-ethyl]-2-naphthalenesulfonamide

The title compound was prepared according to the procedure of Example 3 using (*R*)-α-methyl-histamine as the amine component. The product (R_f 0.18; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white foam: ^{1}H NMR (300Hz, $CDCl_3$) 8.42(1H, br s), 7.93(3H, m), 7.80(1H, m), 7.57(2H, m), 7.52(1H, s), 6.72(1H, s), 3.61(1H, m), 2.72(1H, dd), 1.57(1H, dd), 1.11(3H, d); $[\alpha]_D = +41.8^\circ$ (c=0.91, 1:9 methanol/dichloromethane). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan. Found: C 55.36, H 5.08, N 9.40%; $C_{20}H_{21}N_3O_6S$ requires: C 55.67, H 4.90, N 9.37%.

EXAMPLE 72

N-*[2-(4(5)-Imidazoyl)*-trans-*cyclopropyl]-2-naphthalenesulfonamide*

Step a. *2-(1-(Triphenylmethyl)imidazoyl-4-yl)*-trans-*cyclopropylamine.* [2-(1-(Triphenylmethyl)imidazoyl-4-yl)-*trans*-cyclopropyl]-carbamic acid 1*R*-(2-naphthyl)-ethyl ester was prepared according to Burger's synthesis of the corresponding ethyl ester using *R*-(+)-2-naphthyl ethanol.[5] It was dissolved in 1:1 methanol/tetrahydrofuran and was hydrogenated in the presence of a catalytic quantity

of 10% palladium-on-charcoal at atmospheric pressure and temperature for 18h. Filtration and evaporation of the reaction mixture afforded the amine product.

Step b. N-*[2-(1-(Triphenylmethyl)imidazoyl-4-yl)*-trans-*cyclopropyl]-2-naphthalenesulfonamide* was prepared by the reaction between the product from step a and 2-naphthalenesulfonyl chloride according to the procedure of Example 6 step a.

Step c. The product from step b was deprotected according to the procedure of Example 17 step d and the title compound (R_f 0.26; 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a white foam: ^{1}H NMR (300Hz, $CDCl_3$) 8.44(1H, s), 7.92(3H, m), 7.84(1H, dd), 7.62(2H, m), 7.47(1H, s), 6.72(1H, s), 2.48(1H, m), 2.15(1H, m), 1.27(1H, m), 1.21(1H, m).

EXAMPLE 73

3-(4(5)-Imidazoyl)-2S-(2-naphthalene)sulfonamino -propionic acid methyl ester

Step a. *3-(1-(Triphenylmethyl)imidazoyl-4-yl)-2S-(2-naphthalene)sulfonamino - propionic acid methyl ester.* To a solution of triphenylmethylhistidine methyl ester hydrochloride (488mg, 1.00mmol) and triethylamine (304μl, 2.20mmol) in dry dichloromethane (20ml), under an atmosphere of argon, was added 2-naphthalenesulfonyl chloride (238mg, 1.05mmol). The solution was stirred for 1h, washed with water (2x20ml), dried over magnesium sulfate, filtered and evaporated. The residue was recrystallized from 1:2 ethyl acetate/hexane to afford the product as a white solid (438mg, 73%).

Step b. The product from step a (550mg, 0.91mmol) was deprotected according to the procedure of Example 17 step d and the title compound (R_f 0.32; 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a white solid (114mg, 35%): ^{1}H NMR (300Hz, d_6-DMSO) 11.75(1H, br s), 8.45(1H, d), 8.28(1H, d), 8.09(1H, dd), 8.02(2H, t), 7.68(3H, m), 7.39(1H, d), 6.72(1H, s), 4.08(1H, dd), 3.21(3H, s), 2.76(2H, m). The maleate salt was prepared by lyophilysis of an

equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 74

N-[1S-Hydroxymethyl-2-(4(5)-imidazoyl)ethyl]-2-naphthalenesulfonamide

Step a. *N-[1S-Hydroxymethyl-2-(1-(triphenylmethyl)imidazoyl-4-yl)ethyl]-2-naphthalenesulfonamide.* To a solution of the product from Example 73 step a (438mg, 0.73mmol) in methanol (6ml) and tetrahydrofuran (12ml) was added, with stirring, a mixture of sodium borohydride (378mg, 10.0mmol) and lithium chloride (420mg, 10.0mmol) in small portions over several hours. The mixture was concentrated *in vacuo* and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate and evaporated to give the product as a white foam (305mg, 73%).

Step b. The product from step a (300mg, 0.52mmol) was deprotected according to the procedure of Example 17 step d and the title compound (R_f 0.32; 1:10:90 ammonia(880)/methanol/dichloromethane) was isolated as a white solid (56mg, 33%): ^{1}H NMR (300Hz, d_6-DMSO) 8.34(1H, s), 8.09(1H, d), 8.00(2H, m), 7.67(3H, m), 7.41(1H, d), 6.69(1H, s), 3.25(3H, m), 2.64(1H, dd), 2.46(1H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 75

3-(4(5)-Imidazoyl)-2S-(2-naphthalene)sulfonamino -propionic acid

Step a. *3-(1-(Triphenylmethyl)imidazoyl-4-yl)-2S-(2-naphthalene)sulfonamino -propionic acid.* To a solution of triphenylmethylhistidine (398mg, 1.00mmol) and triethylamine (304μl, 2.20mmol) in dry dichloromethane (20ml), under an atmosphere of argon, was added 2-naphthalenesulfonyl chloride (238mg, 1.05mmol). The solution was stirred for 1h and water (20ml) was added. Dilute acetic acid was added until pH5 was reached. The mixure was shaken. The organic layer was washed with brine, dried over magnesium sulfate and evaporated to give the product as a pale

yellow solid (486mg, 83%).

Step b. A solution of the product from step a (486mg, 0.83mmol) in trifluoroacetic acid (5ml) was stirred for 18h and the solvent evaportated. The residue was triturated with diethyl ether and the resultant white solid recrystallized from propan-2-ol/diethyl ether. The trifluoroacetic acid salt of the title compound (R_f 0.07; 20% methanol/dichloromethane) was isolated as a white solid (115mg, 30%): ^{1}H NMR (300Hz, d_6-DMSO) 8.30(1H, d), 8.00(4H, m), 7.68(3H, m), 6.98(1H, s), 4.06(1H, dd), 2.93(1H, dd), 2.81(2H, dd). Found: C 47.08, H 3.59, N 9.20%; $C_{18}H_{16}F_3N_3O_6S$ requires: C 47.06, H 3.51, N 9.15%.

EXAMPLE 76

N-[5-(4(5)-Imidazoyl)pentyl]-N'-(2-hydroxyethyl)-sulfamide

Step a. *N-[5-(2-(tert-butyldimethylsilyl)-1-(N,''N''-dimethylsulfamoyl)imidazol-4-yl)pentyl]-N'-(2-hydroxyethyl)-sulfamide.* 5-(5-Aminopentyl)-2-(*tert*-butyldimethylsilyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole (Example 54 step a) and 2-bromoethanol were allowed to react with chlorosulfonyl isocyanate according to the procedure of Example 12 step a. A solution of the resultant compound in ethanol was treated with 2M sodium hyroxide (2 equivalents) solution and heated at reflux for 2min and the solvent was evaporated. Water was added to the residue and the mixture extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash column chromatography (silica; 2-4% methanol/dichloromethane) and the product was isolated as a colourless oil.

Step b. The product from step b was deprotected according to the procedure of Example 12 step c. The title compound (R_f 0.35; 1:10:90 ammonia(880)/methanol/dichloromethane)was obtained as a colourless oil: ^{1}H NMR (300Hz, d_6-DMSO) 11.70(1H, br s), 7.46(1H, s), 7.10(1H, t), 6.87(1H, t), 6.68(1H, s), 3.60(2H, t), 3.12(2H, dd), 2.79(2H, dd), 2.46(2H, t), 1.61(2H, quint.), 1.46(2H, quint.), 1.37(2H, quint.).

EXAMPLE 77

N-[4-(4(5)-Imidazoyl)butyl]-(4-bromophenyl)methanesulfonamide

The title compound was prepared according to the procedure for Example 9, using 5-(4-aminobutyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] and (4-bromophenyl)methanesulfonyl chloride (prepared essentially as Example 4 step a) as the substrates in step a. The product of the two steps was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.56(1H, s), 7.47(2H, d), 7.30(2H, d), 7.04(1H, t), 6.69(1H, s), 4.28(2H, s), 2.87(2H, dd), 2.46(2H, m), 1.53(2H, quint.), 1.41(2H, quint.). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 78

N-[4-(4(5)-Imidazoyl)butyl]-(4-trifluoromethylphenyl)methanesulfonamide

The title compound was prepared according to the procedure for Example 9, using 5-(4-aminobutyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] and (4-trifluoromethylphenyl)methanesulfonyl chloride (prepared essentially as Example 4 step a) as the substrates in step a. The product was obtained as a white solid: ^{1}H NMR (300Hz, d_4-MeOH) 7.67(2H, d), 7.60(2H, d), 7.55(1H, s), 6.76(1H, s), 4.39(2H, s), 3.00(2H, t), 2.57(2H, t), 1.64(2H, quint.), 1.48(2H, quint.). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 79

N-[4-(4(5)-Imidazoyl)butyl]-(4-fluoromethylphenyl)methanesulfonamide

The title compound was prepared according to the procedure for Example 9, using 5-(4-aminobutyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole[1] and (4-fluoromethylphenyl)methanesulfonyl chloride (prepared essentially as Example 4 step a) as the substrates in step a. The product was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 7.47(1H, s), 7.39(2H, dd), 7.18(2H, t), 7.01(1H, t), 6.69(1H,

s), 4.28(2H, s), 2.86(2H, dd), 2.48(2H, m), 1.52(2H, quint.), 1.42(2H, quint.). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 80

N-[4-(4(5)-Imidazoyl)butyl]-N'-(1R-phenylethyl)-sulfamide

The title compound was prepared according to the procedure for Example 51, using (*R*)-(+)-α-methylbenzylamine as the substrate in step e. The product (R_f 0.24; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.80(1H, br s), 7.47(1H, s), 7.28(5H, m), 7.21(1H, dd), 6.66(1H, s), 6.65(1H, t), 4.29(1H, m), 2.65(2H, m), 2.40(2H, t), 1.47(2H, m), 1.41(3H, d), 1.36(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 81

N-[4-(4(5)-Imidazoyl)butyl]-N'-(1S-phenylethyl)-sulfamide

The title compound was prepared according to the procedure for Example 51, using (*S*)-(+)-α-methylbenzylamine as the substrate in step e. The product (R_f 0.24; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.80(1H, br s), 7.47(1H, s), 7.28(5H, m), 7.21(1H, dd), 6.66(1H, s), 6.65(1H, t), 4.29(1H, m), 2.65(2H, m), 2.40(2H, t), 1.47(2H, m), 1.41(3H, d), 1.36(2H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 82

N-[5-(4(5)-Imidazoyl)pentyl]-N'-(4-biphenyl)methyl-sulfamide

The title compound was prepared according to the procedure for Example 49, using 5-(5-aminopentyl)-1-(*N*,*N*-dimethylsulfamoyl)-imidazole.[1] The product was obtained as a white solid: ^{1}H NMR (300Hz, d_4-MeOH) 7.60(4H, m), 7.52(1H, s), 7.43(4H,

m), 7.32(1H, dd), 6.72(1H, s), 4.16(2H, s), 2.91(2H, t), 2.55(2H, t), 1.59(2H, quint.), 1.51(2H, quint.), 1.38(2H, quint.).

EXAMPLE 83

N-*[5-(4(5)-Imidazoyl)butyl]*-N'-*(1,1-diphenyl)methyl-sulfamide*

The title compound was prepared according to the procedure for Example 51, using *C,C*-diphenyl methylamine as the substrate in step e. The product (R_f 0.28; 1:10:90 ammonia(880)/methanol/dichloromethane) was obtained as a white solid: ^{1}H NMR (300Hz, d_6-DMSO) 11.70(1H, br s), 8.03(1H, d), 7.46(1H, s), 7.27(10H, m), 6.76(1H, t), 6.63(1H, s), 5.42(1H, d), 2.52(2H, t), 2.32(4H, t), 1.36(2H, quint.), 1.19(2H, quint.). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 84

N-*[4-(4(5)-Imidazoyl)butyl]-(4-biphenyl)methanesulfonamide*

The title compound was prepared according to the procedure for Example 9, using 5-(4-aminobutyl)-1-(*N,N*-dimethylsulfamoyl)-imidazole and (4-biphenyl)methanesulfonyl chloride (prepared essentially as Example 4 step a) as the substrates in step a. The product was obtained as a white solid: ^{1}H NMR (300Hz, d_4-MeOH) 7.63(4H, m), 7.56(1H, s), 7.48(4H, m), 7.32(1H, m), 6.76(1H, s), 4.34(2H, s), 3.00(2H, t), 2.58(2H, t), 1.65(2H, quint.), 1.52(2H, quint.). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

EXAMPLE 85

N-*[4-(4(5)-Imidazoyl)butyl]*-N-*methyl-2-(4-chlorophenyl)ethanesulfonamide*

N-[4-(1-(*N',N'*-Dimethylsulfamoyl)imidazol-4-yl)butyl]-2-(4-chlorophenyl)ethanesulfonamide, an intermediate in the synthesis of Example 55, was methylated with iodomethane essentially as Example 68 step a. Deprotection according to Example 9 step b gave the title compound as a colourless oil: ^{1}H NMR

(300Hz, d_4-MeOH) 7.55(1H, d), 7.27(4H, m), 6.78(1H, s), 3.26(2H, m), 3.21(2H, t), 3.06(2H, m), 2.83(3H, s), 2.63(2H, t), 1.64(4H, m). The maleate salt was prepared by lyophilysis of an equimolar solution of the product and maleic acid in water/dioxan.

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5. A. Burger, M. Bernabé, P.W. Collins *J. Med. Chem.* 1970, **13**, 33.H_3 receptor bioassay

The biological activity of the compounds of the examples was measured using the ileal longitudinal muscle, myenteric plexus assay described by Paton and Aboo Zar (J. Physiol. 194, 13-33 (1968)). Male Dunkin-Hartley guinea pigs (250-300g) were employed. Briefly, a 50cm portion of ileum proximal to the caecum was removed, after discarding the terminal 20cm. Ileal segments (3cm) were cleaned by passing Krebs-Henseleit buffer containing 3μM mepyramine gently through the ileum using a Pasteur pipette (size: 13.8cm length, 0.65cm diameter). To avoid unnecessary damage to the tissue, Krebs-Henseleit buffer was passed through the ileal segment, while it was lying horizontally on a petri dish. Therefore, the ileum was not over-distended and the buffer flowed through with ease. Each segment was then passed over a Pasteur pipette and the longitudinal muscle layer and adhering myenteric plexus was teased away using moist cotton wool, by stroking tangentially away from the mesenteric attachment. The tissues were suspended in 20ml organ baths containing Krebs-Henseleit buffer at 37$\pm$1°C and gassed with 95%CO_2/5%O_2. The tissues were ligated to two parallel stainless steel wires, situated between two platinum electrodes (0.76cm length, 0.06cm diameter). All measurements were recorded isometrically (Grass FTO3 transducer). Following an initial loading tension of 1g, the tissues were

stimulated with electrical pulses at a frequency of 0.1Hz and a pulse duration of 0.5msec, as described by Kosterlitz & Watt (1968). Initially, the tissues were stimulated at supramaximal (1.3 fold times maximal) voltage for a period of 30 min and then the tissues were washed and re-stimulated. A "sighter dose" of the selective histamine H_3-receptor agonist, R-(α)-methylhistamine (0.3μM) (Arrang *et al.*, 1987), was administered. Upon generation of response, the "sighter dose" was removed from the tissues by "washout" (6 washes over 60 min) and during this period the electrical stimulation was switched off. The tissues were then re-stimulated and allowed to stabilise prior to the addition of drug treatments, which were allocated on a randomised block basis to the organ baths. Following the incubation period, a single cumulative E/[A] curve was obtained. The experimental E/[A] curve data was expressed as the percentage inhibition of the peak height of electrically-stimulated contraction. Antagonist affinity values were calculated from the degree of rightward shift of the R-(α)-methylhistamine E/[A] curves using Schild's methods (Arunlatcshama & Schild, 1949).

Histamine H_3 radioligand binding assay

Preparation of membranes

Male Dunkin Hartley guinea pigs (200-300g) were used. The small intestine was rapidly removed (cut ~5cm from caecum and 5cm from stomach) and placed in ice-cold 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C). The tissue was cut into ~10cm segments, flushed through with ice-cold 20mM Hepes-NaOH buffer and placed in a beaker containing fresh buffer at 4°C. 10cm segments of ileum were threaded onto a glass pipette and the longitudinal muscle myenteric plexus was peeled away from the circular muscle using damp cotton-wool. Longitudinal muscle myenteric plexus was immediately placed in ice-cold Viaspan® solution (~100ml for tissue from 3 guinea pigs) and placed in the refrigerator for 24 hours.

Pre-soaked tissue was weighed and minced with scissors. The tissue was then homogenised in Viaspan using a polytron (Kinematica AG; PT-DA 3020/2TS, 3 x ~1-2s). 50ml of 500mM Tris HCl (pH6.9 at 21±3°C) was added to the tissue

and the mixture centrifuged at 39,800 x g for 12 min at 4°C. The supernatant was discarded and rehomogenised in 100ml ice-cold 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C) using a teflon-in-glass homogeniser (setting 10; 3 x). The homogenate was recentrifuged at 39,800 x g and the pellet resuspended in 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C), to a tissue concentration of 50mg.ml^{-1}, using a polytron (Brinkman, PT10, 3 x ~1s).

Incubation conditions

Guinea pig ileum longitudinal muscle myenteric plexus membranes (400µl) were incubated for 165 min at 21±3°C in a final volume of 500µl with 20mM Hepes-NaOH buffer containing [^{3}H]-R-α-methylhistamine (50µl; 3nM) and competing compound. Total and non-specific binding of [^{3}H]-R-α-methylhistamine were defined using 50µl of buffer and 50µl of 10µM thioperamide, respectively. The assay was terminated by rapid filtration through Whatman GF/B filters, presoaked (2hr) in 0.1% polyethyleneimine, using a Brandell Cell Harvester. The filters were washed (3 x 3ml) with ice-cold 50mM Tris-HCl (pH6.9 at 21±3°C), transferred into scintillation vials, 5ml liquid scintillation cocktail was added and after 4 hours the bound radioactivity was determined by counting (4 min) in a Beckman liquid scintillation counter.

Data analysis

Data are analysed using GraphPad prism and the general equation for a competition curve with variable Hill slope (n_H).

$$Y = \text{Non-specific binding} + \frac{\text{(Total binding - Non-specific binding)}}{1+10^{((\log IC_{50}-X).n_H)}}$$

where

X is the log concentration of competing compound,

Y is the binding obtained at each concentration of X,

pIC_{50} is the concentration of the competitor required to compete for half of the specific binding.

The IC_{50} is converted to the K_i using the Cheng Prusoff equation,

$$K_I = IC_{50}/(1+(L/K_D))$$

where

IC_{50} is the concentration of competitor required to compete for half the specific binding,

L is the radioligand concentration used,

K_D is the equilibrium dissociation constant for the radioligand determined by saturation experiments.

The following results were obtained in the two assays:

Example No.	pK_B (functional assay)	pK_I (binding assay)
1	6.70	7.77
2	5.62	
3	6.27	
4	6.40	
6	6.96	7.50
7	6.81	7.42
8	7.11	7.49
9	7.33	7.94
10	8.62	8.53
11	8.01	7.95
12	8.20	8.23
13	8.68	8.56
14	7.04	7.28
15	8.77	8.36
16	6.77	
17	6.35	
18	6.79	
19	< 5.0	5.95
20	< 5.50	7.26
21	< 5.0	5.54
23	5.87	7.55
26	6.29	

Example No.	pK_B (functional assay)	pK_I (binding assay)
27	5.11	
28	5.39	
29	6.88	7.40
30	6.62	6.97
31	5.79	7.07
32	7.36	7.44
33	6.64	7.27
34		7.23
35	5.59	
36	6.16	
37	5.71	
38	8.37	8.15
39	7.37	7.80
40		6.02
41	8.41	8.37
42	7.86	7.79
43	6.42	7.25
44	8.49	8.68
45	8.91	8.71
46	7.70	7.84
47	8.48	8.57
48	7.06	7.58

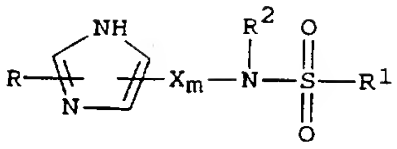
Example No.	pK_B (functional assay)	pK_I (binding assay)
49	8.32	8.12
50	7.73	7.78
51	7.01	7.10
52		6.70
53	6.74	7.25
54	7.80	8.00
55	8.22	8.11
56	6.35	6.86
57	7.96	7.84
58	8.98	8.36
59	8.43	8.08
60	7.84	8.34
61	8.62	8.46
62	8.13	8.24
63	8.39	8.18
64	8.41	8.30
65	7.32	7.98
66	8.06	8.11
67	6.22	6.85
68	7.77	7.95
69	8.92	8.73
70	7.80	7.95

Example No.	pK_B (functional assay)	pK_i (binding assay)
71	$p[A]_{50}=6.11$	8.44
72	6.02	
73	4.99 $\alpha \sim 20\%$	
77		8.51
78		8.45
79		8.13
80		6.76
81		6.84
82		7.56
84	8.10	
85	8.05	

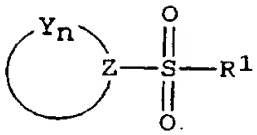
Typical variance in the functional assay is $\pm$ 0.15 log units. Typical variance in the binding assay is $\pm$ 0.12 log units. This means that if the discrepancy between the two assays is greater than about 0.5 log units, then this difference on average is significant.

CLAIMS.

1. A compound of the formula



or



wherein

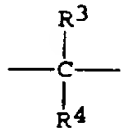
R represents from zero to two substituents,

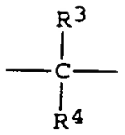
R^1 is C_4 to C_{20} hydrocarbyl (in which one or more hydrogen atoms may be replaced by halogen, and up to four carbon atoms may be replaced by oxygen, nitrogen or sulphur atoms, provided that R^1 does not contain an -O-O- group),

R^2 is H or C_1 to C_{15} hydrocarbyl (in which one or more hydrogen atoms may be replaced by halogen, and up to three carbon atoms may be replaced by oxygen, nitrogen or sulphur atoms, provided that R^2 does not contain an -O-O- group),

m is from 1 to 15

n is from 2 to 6,

each X group is independently  , or one X group is -N(R^4)-, -O- or -S- (provided that this X group is not adjacent the -NR^2- group) and the

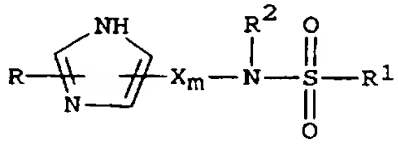
remaining X groups are independently  , wherein R^3 is H, C_1 to C_6 alkyl, C_2 to C_6 alkenyl, $-CO_2R^5$, $-CONR^5_2$, $-CR^5_2OR^6$ or $-OR^5$ (in which R^5 and R^6 are H or C_1 to C_3 alkyl), and R^4 is H or C_1 to C_6 alkyl,

each Y group is independently $-C(R^3)R^4-$, or up to two Y groups are $-N(R^4)-$, -O- or -S- and the remaining Y groups are independently $-C(R^3)R^4-$, wherein R^3 is as defined above, one R^4 group in the structure is imidazoyl, imidazoylalkyl, substituted imidazoyl or substituted imidazoylalkyl, and the remaining R^4 groups are H or C_1 to C_6 alkyl, and

Z is $>C(R^7)NR^2-$ or $>N-$, wherein R^7 is any of the groups recited above for R^3,

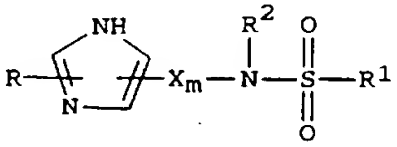
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 having the formula



wherein $-X_m-$ is attached to the 4- or 5- position of the imidazole ring.

3. A compound according to claim 1 or claim 2 having the formula



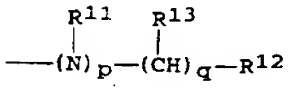
wherein m is at least 3.

4. A compound according to claim 2 or claim 3 wherein $-X_m-$ is a C_3 to C_9 alkylene group.

5. A compound according to any preceding claim wherein R^2 is H, C_1 to C_6 alkyl, C_1 to C_6 cycloalkyl, C_1 to C_6 hydroxyalkyl, C_1 to C_6 alkylhydroxyalkyl, aryl C_1 to C_6 alkyl or substituted aryl C_1 to C_6 alkyl.

6. A compound according to claim 5 wherein R^2 is hydrogen or C_1 to C_3 alkyl.

7. A compound according to any preceding claim wherein R^1 is a group of the formula



wherein

p is 0 or 1,

R^{11} is H or C_1 to C_3 alkyl,

q is from 0 to 4,

R^{12} is a carbocyclic, substituted carbocyclic, heterocyclic or substituted heterocyclic group, and

R^{13} is independently selected from H, C_1 to C_6 alkyl, C_1 to C_6 cycloalkyl, C_1 to C_6 hydroxyalkyl, C_1 to C_6 alkylhydroxyalkyl, aryl C_1 to C_6 alkyl and substituted aryl C_1 to C_6 alkyl.

8. A compound according to claim 7 wherein R^{13} is H.

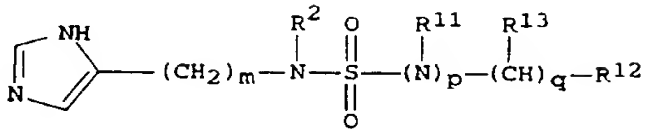
9. A compound according to any of claims 1 to 8 wherein R^1 contains an aryl or substituted aryl group.

10. A compound according to claim 9 wherein the aryl group is phenyl or substituted phenyl.

11. A compound according to claim 9 wherein the aryl group is naphthyl or

substituted naphthyl.

12. A compound according to claim 1 having the formula



wherein m is from 3 to 10,

R^2 and R^{11} are independently H or methyl,

p is 0 or 1,

q is from 0 to 3,

R^{12} is selected from 2-naphthyl, phenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-iodophenyl, 4-bromophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl, 4-methoxyphenyl, 4-biphenyl, cyclohexyl and adamantyl, and

R^{13} is independently selected from H, methyl and phenyl.

13. A compound according to any of claims 1 to 8 wherein R^1 is a (cycloalkyl)alkyl group.

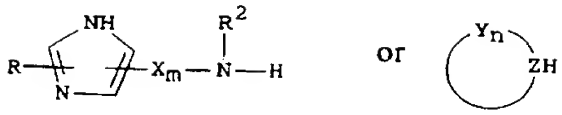
14. A compound according to claim 13 wherein the (cycloalkyl)alkyl group is cyclohexylpropyl or adamantylpropyl.

15. A compound according to any preceding claim wherein m is from 3 to 9.

16. A compound which is degraded *in vivo* to yield a compound according to any preceding claim.

17. A pharmaceutical composition comprising a compound according to any preceding claim and a pharmaceutically acceptable excipient or carrier.

18. A method of making a compound according to claim 1, said method comprising reacting a suitably protected derivative of a compound of the formula

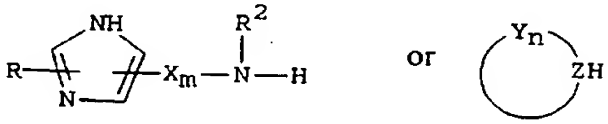


with a sulfonyl chloride of the formula R^1SO_2Cl, wherein R, R^1, R^2, X, Y, Z, m and n are as defined in any of claims 1 to 15.

19. A method of making a sulfamide compound according to claim 1, said method comprising the steps of

a) reacting chlorosulfonyl isocyanate with an appropriate alcohol,

b) reacting the product of step a) with a suitably protected derivative of a compound of the formula

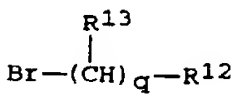


c) reacting the product of step b) with a base such as sodium hydride and then a compound of formula R^1-Br, wherein the bromine atom is attached to a carbon atom of R^1, and

d) treating the product of step c) with acid,

wherein R, R^1, X, Y, Z, m, n and R^2 are as defined in any of claims 1 to 15.

20. A method according to claim 19 wherein the compound of formula R^1-Br used in step c) is of the formula



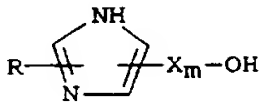
wherein q, R^{12} and R^{13} are as defined in claim 7.

21. A method of making a sulfamide compound according to claim 1, said method comprising the steps of

a) reacting chlorosulfonyl isocyanate with an appropriate alcohol,

b) reacting the product of step a) with a suitably protected derivative of a compound of the formula R^1-H, wherein the hydrogen atom is attached to a nitrogen atom of R^1,

c) reacting the product of step b) with a suitably protected derivative of a compound of formula

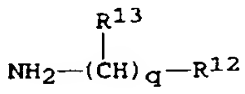


and

d) treating the product of step c) with acid,

wherein R, R^1, X and m are as defined in any of claims 1 to 15.

22. A method according to claim 21 wherein the compound of formula R^1-H used in step b) is of the formula



wherein q, R^{12} and R^{13} are as defined in claim 7.

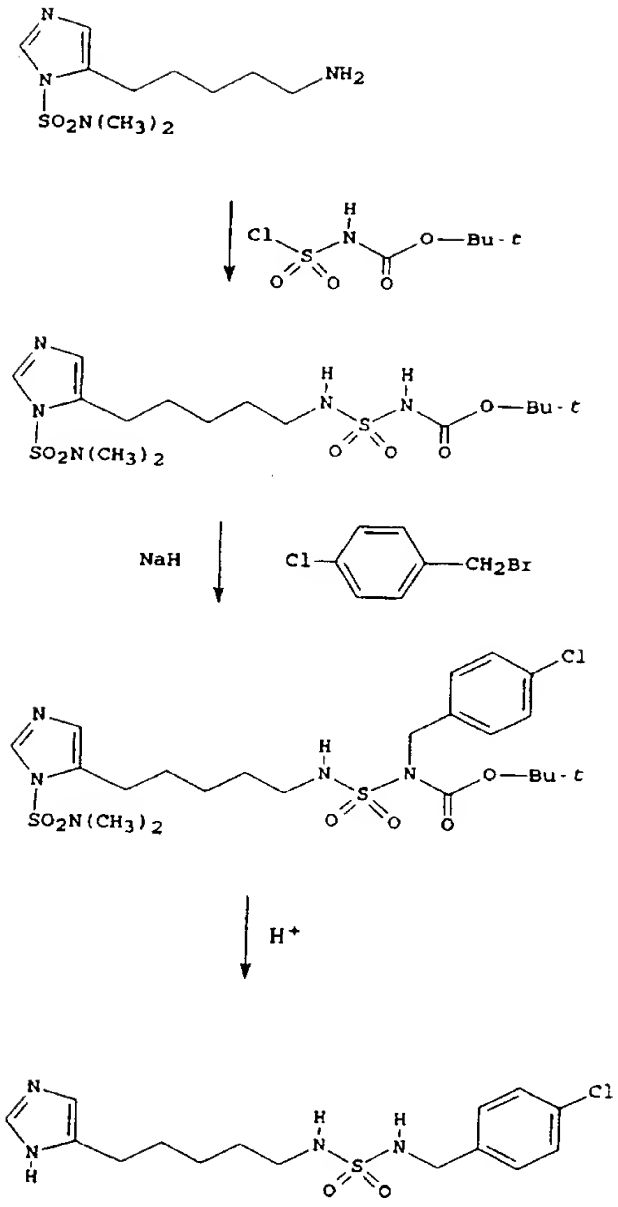


FIGURE 1

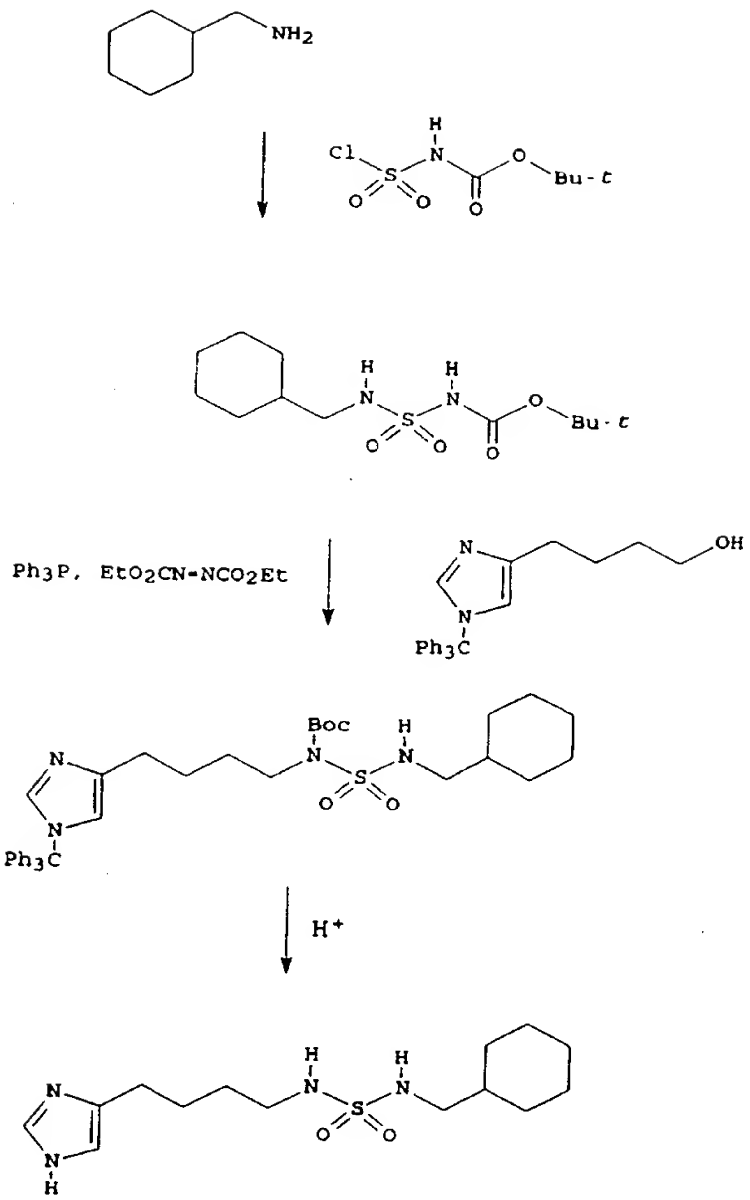


FIGURE 2

INTERNATIONAL SEARCH REPORT

.onal Application No
PCT/GB 97/00358

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D233/54 A61K31/415 C07D401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 447 728 A (MILSTEIN S J ET AL) 5 September 1995 see column 7; example 1, table 1, 10th entry --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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1

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 1997	27. 05. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Fink, D

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 117, no. 16, 19 October 1992 Columbus, Ohio, US; abstract no. 163157, LEE S H ET AL: "Systematic study on the resolution of derivatized amino acids enantiomers on different cyclodextrin-bonded stationary phases" XP002030838 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCE INDEX, vol. 117, 1992, page 4965CS: RN [143455-35-0] and [143455-18-9], and page 4970CS: RN [97685-01-3] & J. CHROMATOGR. (JOCRAM,00219673);92; VOL.603 (1-2); PP.83-93, UNIV. MISSOURI;DEP. CHEM.; ROLLA; 65401; MO; USA (US), ---	1,2
X	CHEMICAL ABSTRACTS, vol. 116, no. 24, 15 June 1992 Columbus, Ohio, US; abstract no. 247605, NISHIZAWA H ET AL: "Enantioseparation of N-dansyl-DL-amino acids by polyacrylamide gel zone electrophoresis" XP002030839 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCE INDEX, vol. 116, 1992, page 5046C: RN [141425-86-7], page 5047CS: RN [132328-69-9], and page 5051CS: RN [7293-13-2] & ANAL. SCI. (ANSCEN,09106340);91; VOL.7 (6); PP.959-61, KYORITSU COLL. PHARM.;TOKYO; 105; JAPAN (JP), ---	1,2
X	J. ANTIBIOT. (JANTAJ,00218820);91; VOL.44 (1); PP.76-85, BRISTOL-MYERS SQUIBB RES. INST.;TOKYO; 153; JAPAN (JP), XP002030833 IMAE K ET AL: "Synthesis, stereochemistry, and biological properties of the depigmenting agents, melanostatin, feldamycin and analogs" see page 77; scheme 1, the compounds no. 5 and 6 --- -/--	1,2

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 113, no. 18, 29 October 1990 Columbus, Ohio, US; abstract no. 164723, TOCHILKIN A I ET AL: "8-Methoxy-5-quinolinesulfonyl chloride, a new fluorogenic reagent for the detection of amines and amino acids" XP002030840 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCES, 12th Collective Index, vol. 106-115, 1987-1991, page 44652CS: RN [129660-67-9] & BIOORG. KHIM. (BIKHD7,01323423);90; VOL.16 (7); PP.956-62, INST. BIOL. MED. CHEM.;MOSCOW; USSR (SU), ---	1,2
X	SYNTHESIS (SYNTBF,00397881);89; (11); PP.825-9, WEIZMANN INST. SCI.;DEP. ORG. CHEM.; REHOVOT; 76100; ISRAEL (IL), XP002030834 WARSHAWSKY A ET AL: "Ring cleavage of N-acyl- and N-(arylsulfonyl)histamines with di-tert-butyl dicarbonate. A one-pot synthesis of 4-acylamino- and 4-arylsulfonylamino-1,2-diaminobutanes" see page 825, column 2, the compounds no. 2b and 2c ---	1,2
X	TETRAHEDRON LETT. (TELEAY,00404039);88; VOL.29 (40); PP.5147-50, FUJISAWA PHARM. CO., LTD.;EXPLOR. RES. LAB.; TSUKUBA; 300-26; JAPAN (JP), XP002030835 SHIGEMATSU N ET AL: "Structure and synthesis of FR900490, a new immunomodulating peptide isolated from a fungus" see page 5150; the compounds no. 5 amd 6 ---	1,2
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	CHEMICAL ABSTRACTS, vol. 56, no. 5, 5 March 1962 Columbus, Ohio, US; abstract no. 4863e, S.B. SEREBRYANYI ET AL: ""Esters of Nalpha-arylsulfonyl amino acids."" XP002030844 see abstract & KHIM. ZHUR. , vol. 27, 1981, pages 365-369, ---	1,2
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X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH, Frankfurt DE XP002030845 see the compounds with the BRN: 47472, 56905, 69186, and 70203 & GAZZ. CHIM. ITAL., vol. 71, 1941, pages 343-349, ---	1,2
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A	WO 95 06037 A (VRIJE UNIVERSITEIT ;VOLLINGA ROELANT CHRISTIAAN (NL); MENGE WIRO M) 2 March 1995 cited in the application see page 24 - page 29; claim 1 ---	1-22

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	TETRAHEDRON LETT. (TELEAY,00404039);96; VOL.37 (34); PP.6209-6212, UNIV. WOLLONGONG;DEP. CHEMISTRY; WOLLONGONG; 2522; AUSTRALIA (AU), XP002030837 UNG A T ET AL: "Synthesis of fluorescent and biotinylated analogs of (1R,2S,3R)-2-acetyl-4(5)-(1,2,3,4-tetrahydroxybutyl)imidazole" see page 6211; compound no. 12a	1

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/GB 97/00358

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,3-11,13-22
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see annex

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

As the drafting of independent claim 1 encompasses such an enormous amount of compounds, a complete novelty search is not possible on economic grounds (see WIPO : "PCT Search Guidelines", November 18, 1992, Part B, Chapter III, item 2).

Therefore, the search - as far as novelty is concerned - had to be limited to the compounds of general formula I, wherein the -X $-NR^2-SO_2-R1$ moiety is attached to the 4- or 5- position of the imidazole ring, i.e. the compounds of present claim 2.

INTERNATIONAL SEARCH REPORT

[redacted]mation on patent family members

[redacted]nal Application No
[redacted]CT/GB 97/00358

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